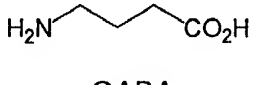
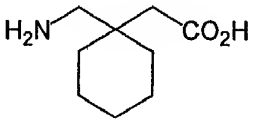
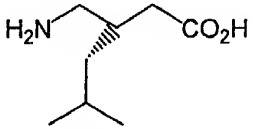
Figure 1



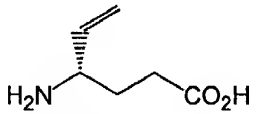
GABA
(1)



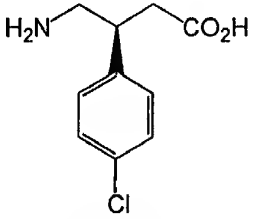
Gabapentin
(2)



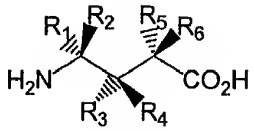
Pregabalin
(3)



Vigabatrin
(4)



Baclofen
(5)



Generalized GABA Analog

(IV)

Figure 2

The Enterohepatic Circulation with Key Transporter Proteins Mediating Bile Acid Circulation

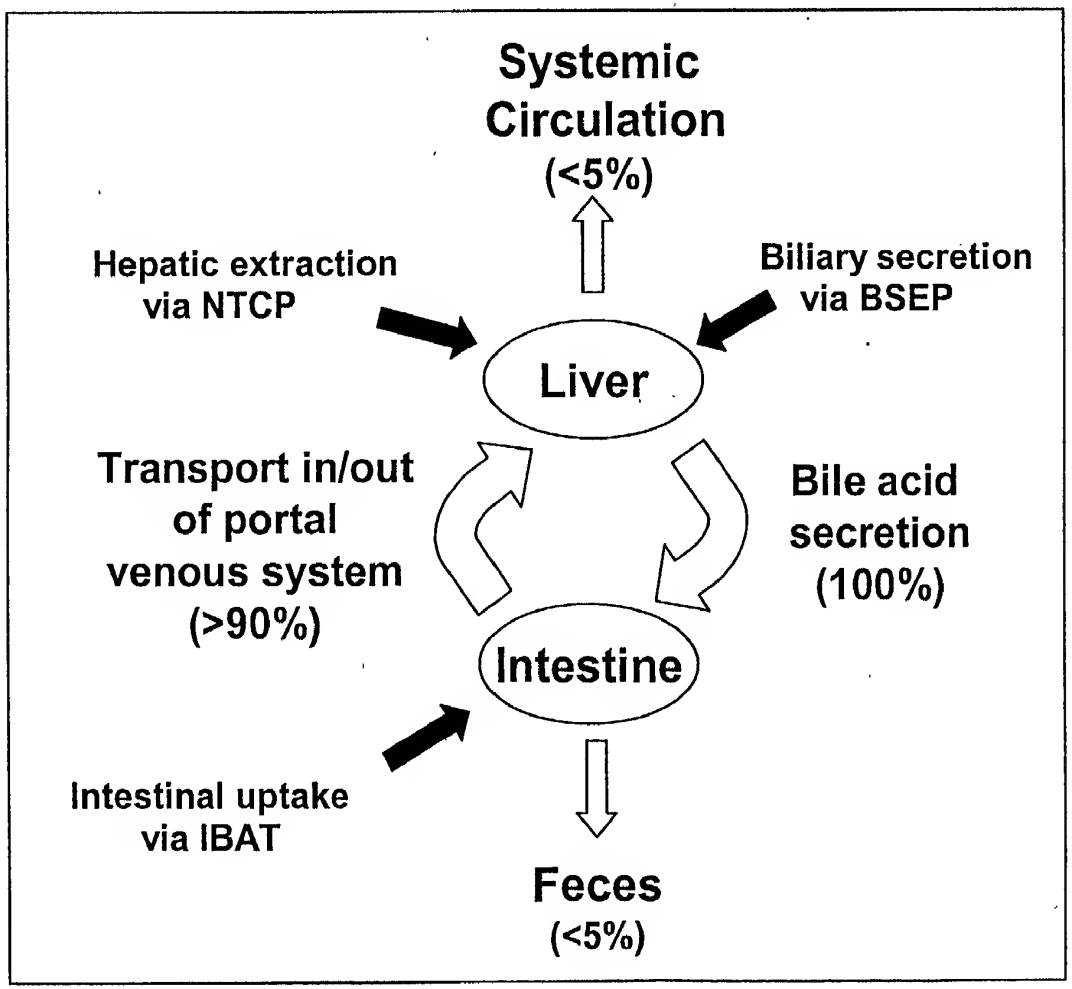
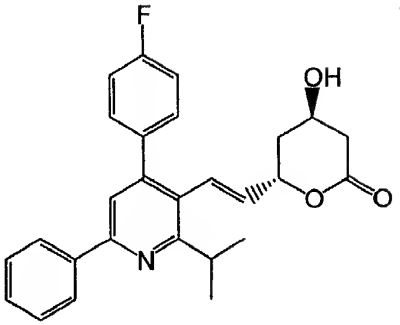
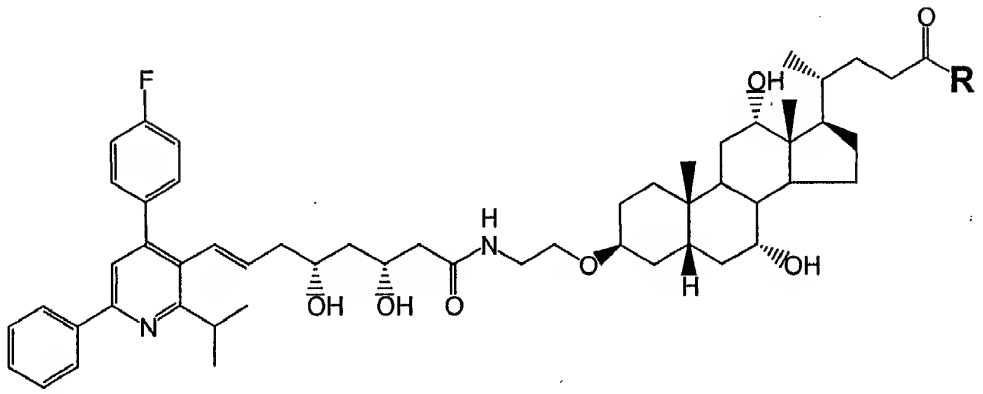


Figure 3

Bile Acid Conjugates of HMG-CoA Reductase Inhibitor



HR 780

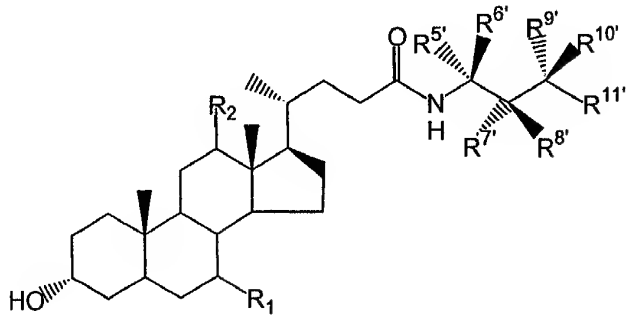


R = OH S 3554

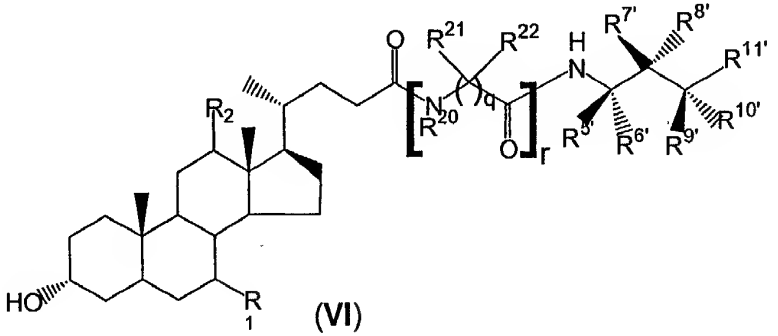
R = $NHCH_2CO_2H$ S 3898

R = $NHCH_2CH_2SO_3H$ S 4193

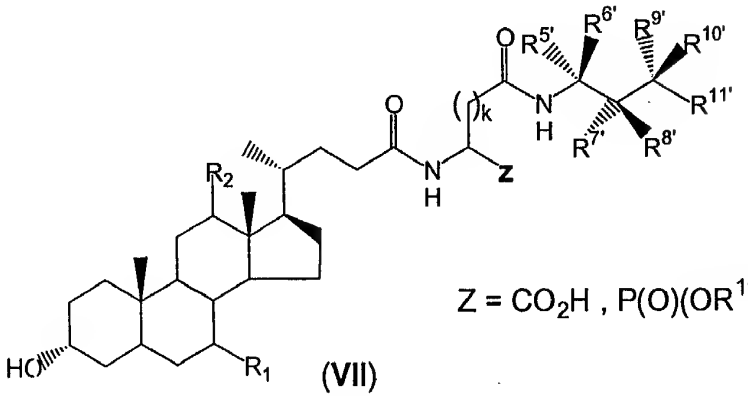
Figure 4



(V)

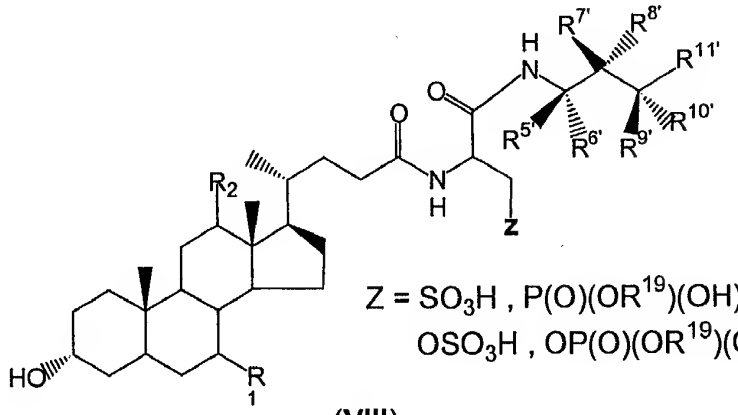


(VI)



Z = CO_2H , $P(O)(OR^{19})(OH)$

(VII)

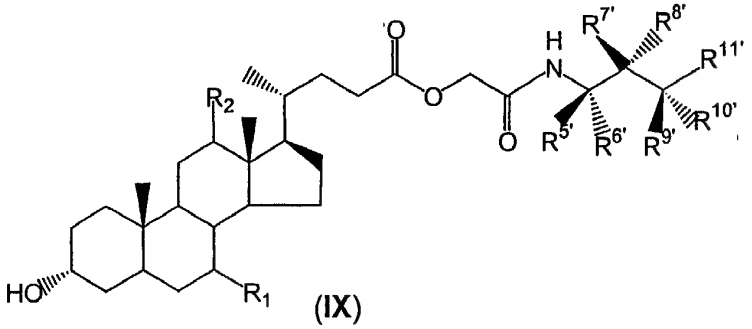


Z = SO_3H , $P(O)(OR^{19})(OH)$, OSO_3H , $OP(O)(OR^{19})(OH)$

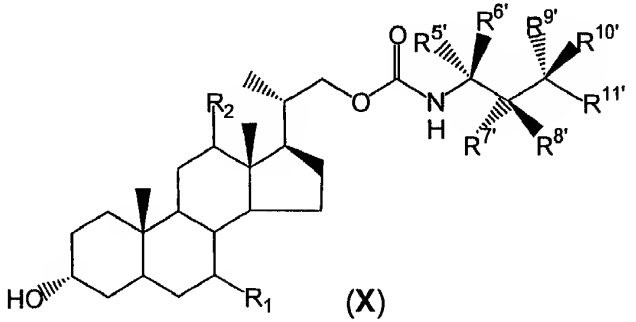
(VIII)

R1 = α-OH ; R2 = α-OH (Cholate)
R1 = β-OH ; R2 = H (Ursodeoxycholate)
R1 = α-OH ; R2 = H (Chenodeoxycholate)
R1 = H ; R2 = α-OH (Deoxycholate)
R1 = β-OH ; R2 = α-OH (Ursocholate)
R1 = H ; R2 = H (Lithocholate)

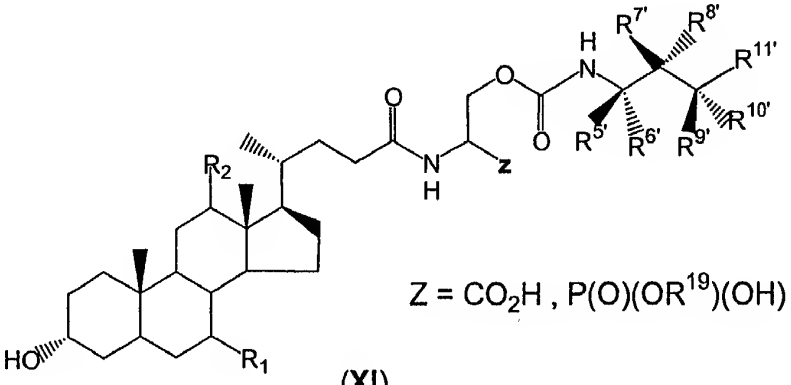
Figure 5



(IX)

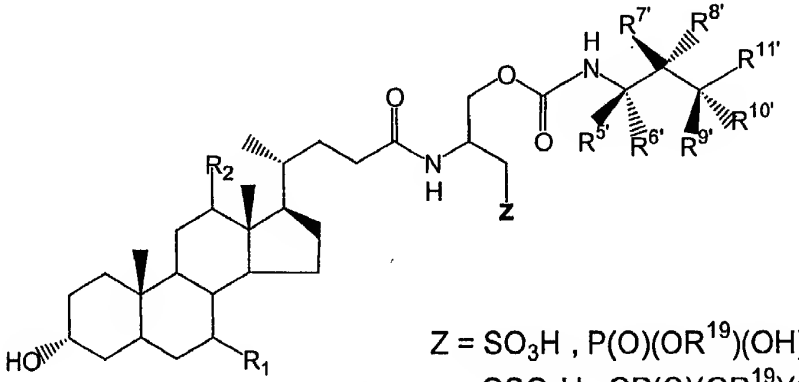


(X)



(XI)

Z = CO_2H , $P(O)(OR^{19})(OH)$

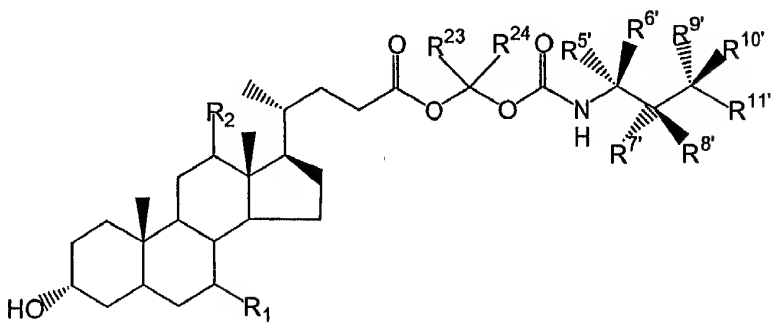


(XII)

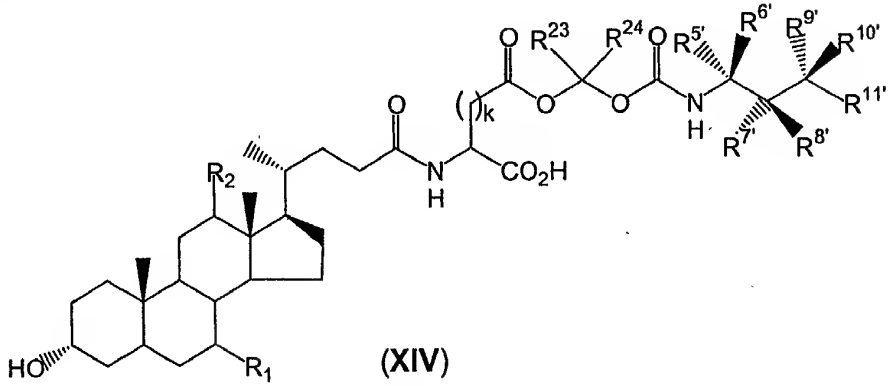
Z = SO_3H , $P(O)(OR^{19})(OH)$, OSO_3H , $OP(O)(OR^{19})(OH)$

R1 = α-OH ; R2 = α-OH (Cholate)
R1 = β-OH ; R2 = H (Ursodeoxycholate)
R1 = α-OH ; R2 = H (Chenodeoxycholate)
R1 = H ; R2 = α-OH (Deoxycholate)
R1 = β-OH ; R2 = α-OH (Ursocholate)
R1 = H ; R2 = H (Lithocholate)

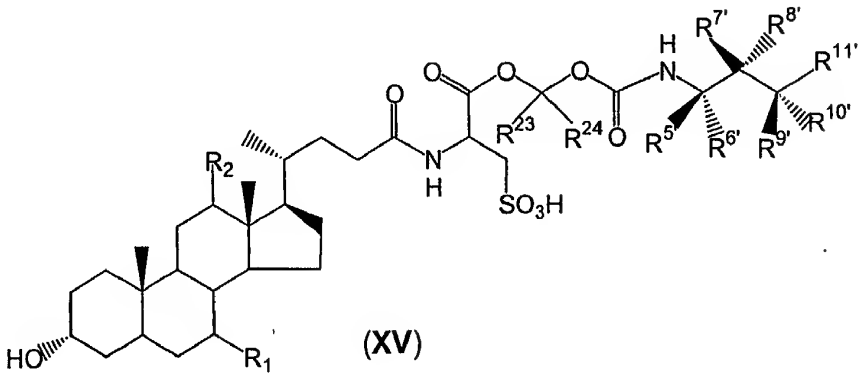
Figure 6



(XIII)



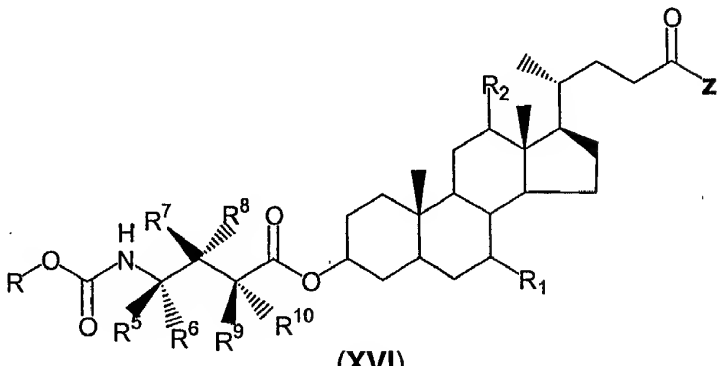
(XIV)



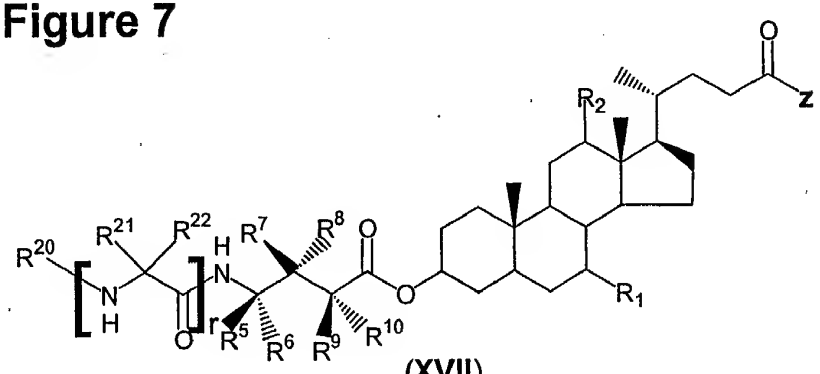
(XV)

R1 = α-OH ; R2 = α-OH (Cholate)
R1 = β-OH ; R2 = H (Ursodeoxycholate)
R1 = α-OH ; R2 = H (Chenodeoxycholate)
R1 = H ; R2 = α-OH (Deoxycholate)
R1 = β-OH ; R2 = α-OH (Ursocholate)
R1 = H ; R2 = H (Lithocholate)

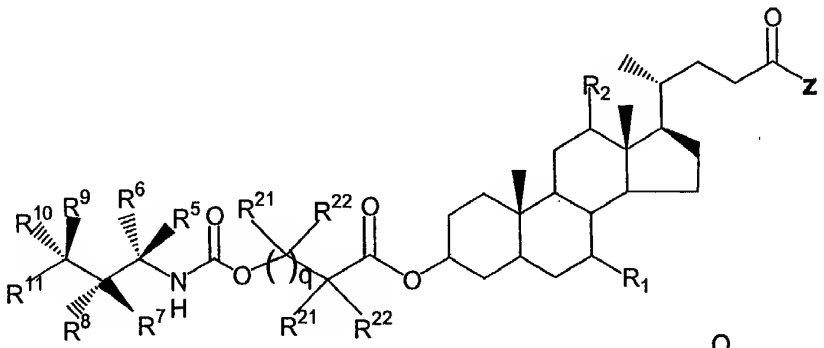
Figure 7



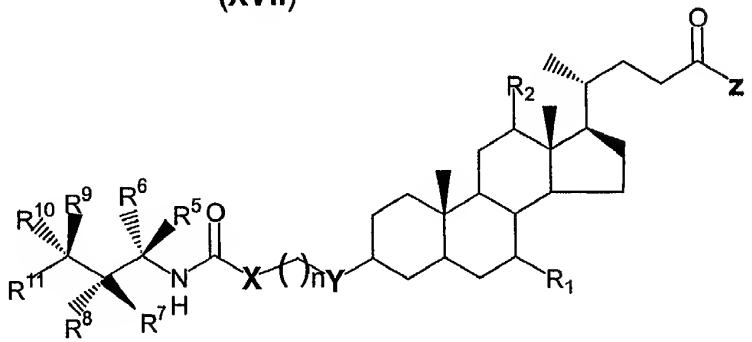
(XVI)



(XVII)

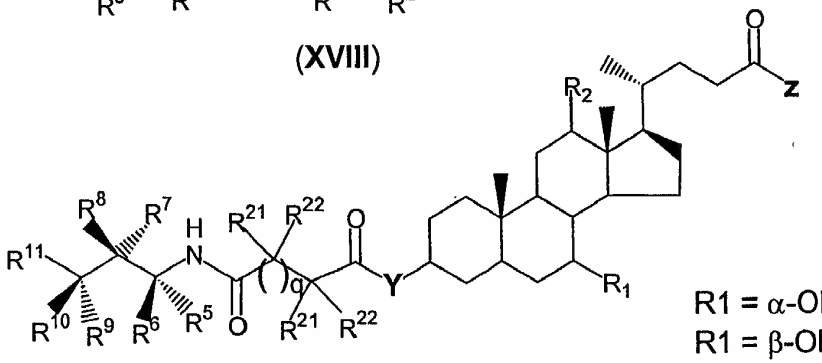


(XVIII)



X = C , O

(XIX)

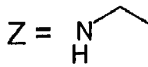


(XX)

R1 = α-OH ; R2 = α-OH (Cholate)
R1 = β-OH ; R2 = H (Ursodeoxycholate)
R1 = α-OH ; R2 = H (Chenodeoxycholate)
R1 = H ; R2 = α-OH (Deoxycholate)
R1 = β-OH ; R2 = α-OH (Ursocholate)
R1 = H ; R2 = H (Lithocholate)

Y = α-O
Y = β-O
Y = α-NH
Y = β-NH

Z = OH

Z = 

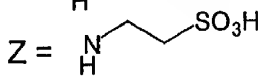
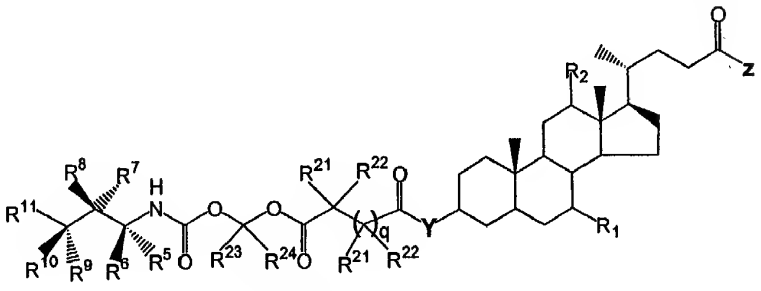
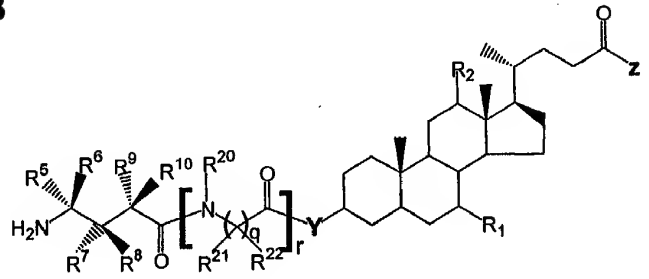
Z = 

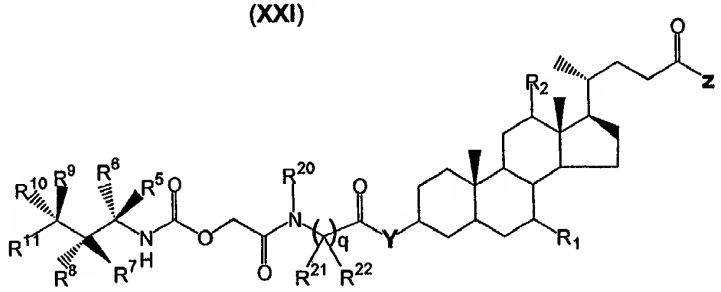
Figure 8



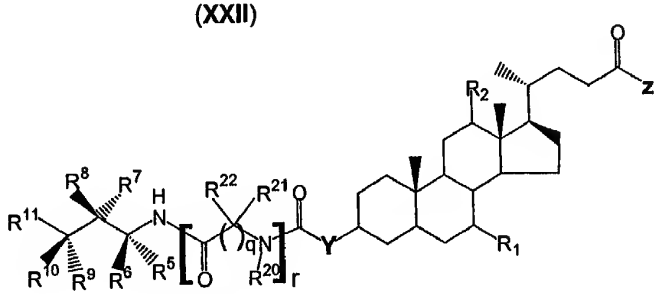
(XXI)



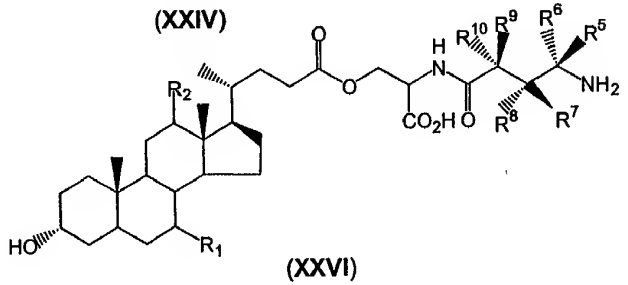
(XXII)



(XXIII)



(XXIV)

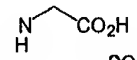


(XXVI)

R1 = α-OH ; R2 = α-OH (Cholate)
R1 = β-OH ; R2 = H (Ursodeoxycholate)
R1 = α-OH ; R2 = H (Chenodeoxycholate)
R1 = H ; R2 = α-OH (Deoxycholate)
R1 = β-OH ; R2 = α-OH (Ursocholate)
R1 = H ; R2 = H (Lithocholate)

Y = α-O
Y = β-O
Y = α-NH
Y = β-NH

Z = OH

Z = 

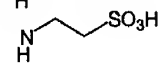
Z = 

Figure 9: Uptake of (8) (XP10569) or Glycochocholate by IBAT-Transfected CHO Cells

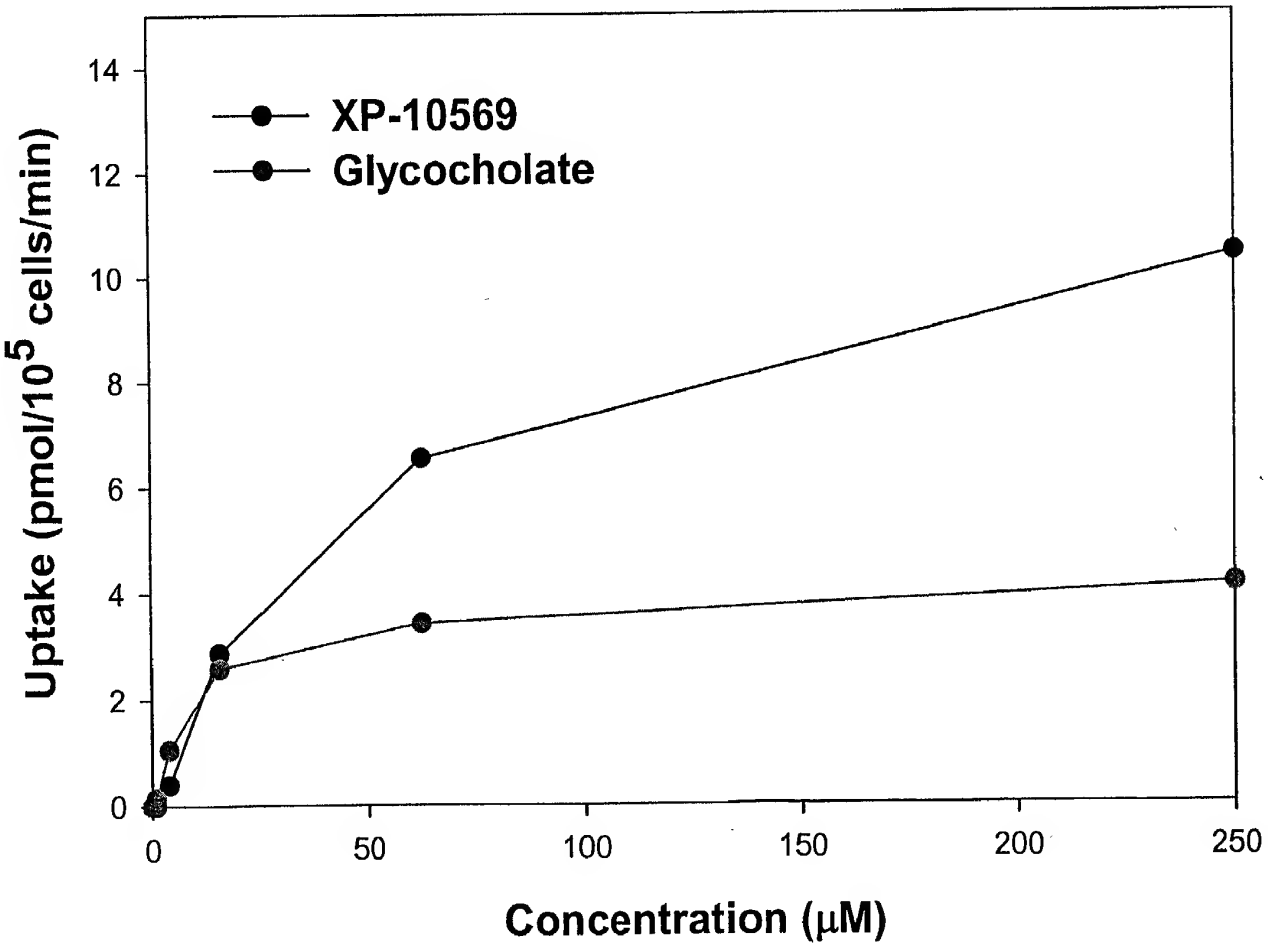


Figure 10: Uptake of (8) (XP10569) or Glycocholate by LBAT-Transfected CHO Cells

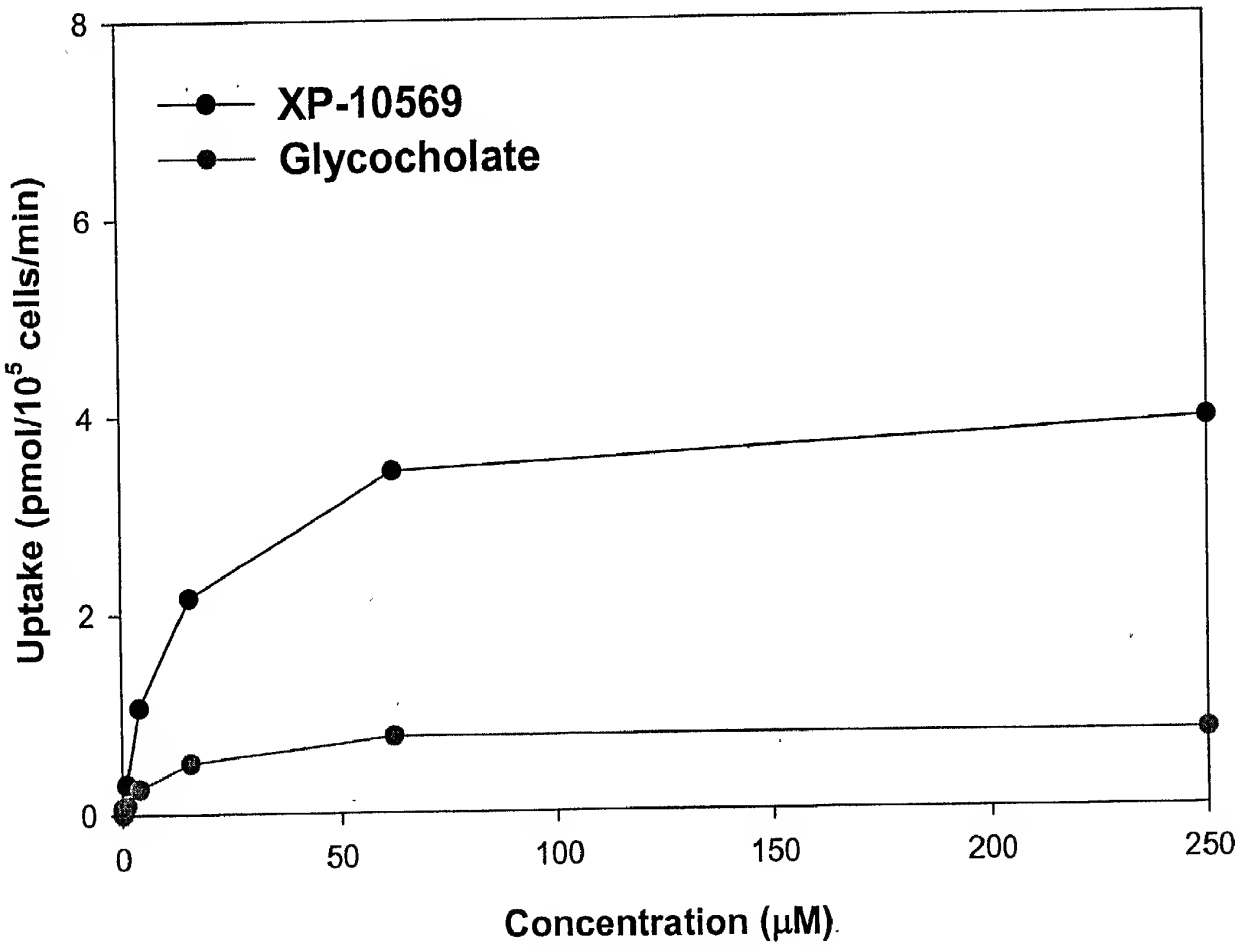


Figure 11

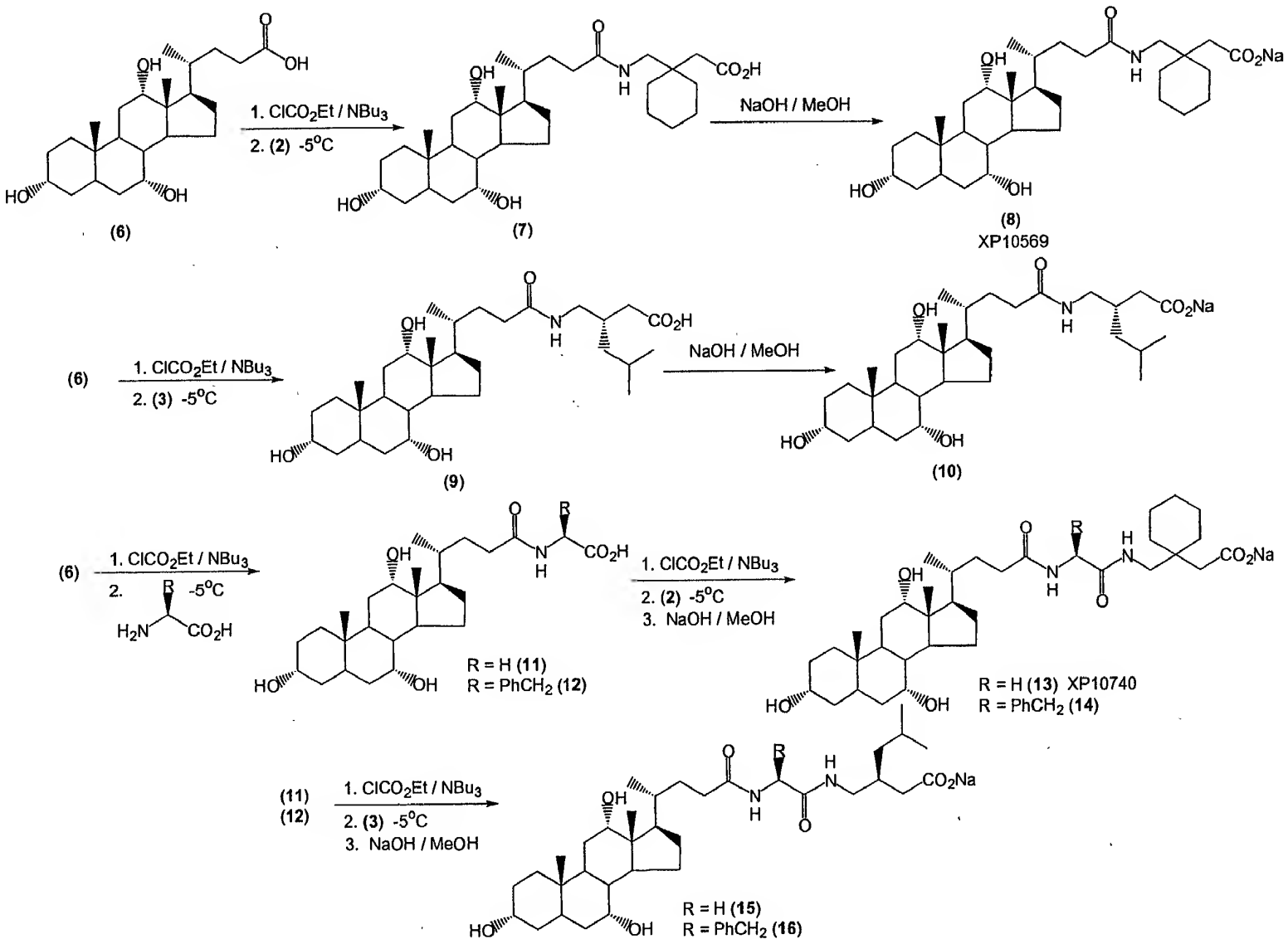


Figure 12

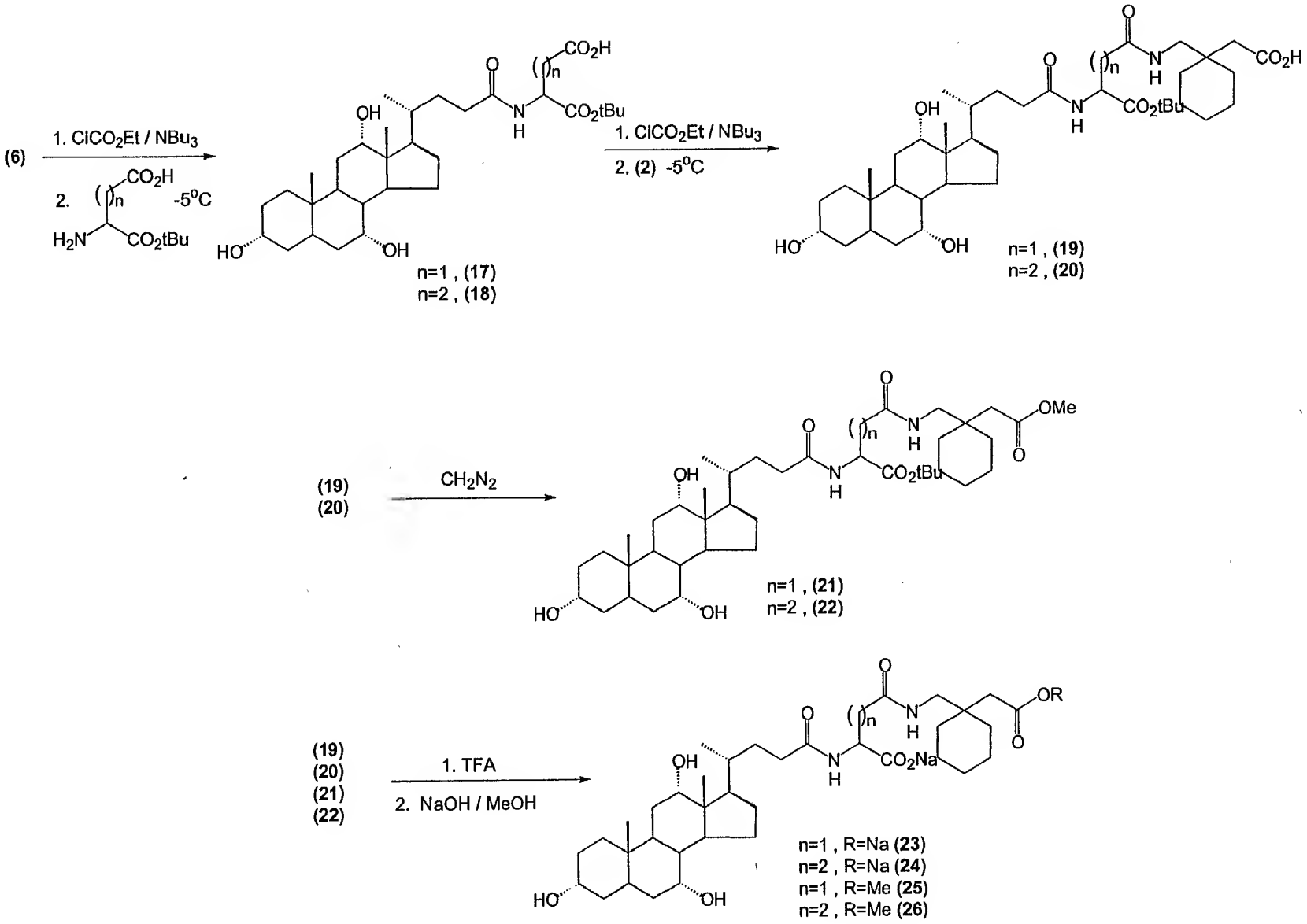

(6)
1. ClCO2Et / NBu3
2. -5°C
n=1 , (17)
n=2 , (18)
1. ClCO2Et / NBu3
2. (2) -5°C
n=1 , (19)
n=2 , (20)
(19)
(20)
CH2N2
n=1 , (21)
n=2 , (22)
(19)
(20)
(21)
(22)
1. TFA
2. NaOH / MeOH
n=1 , R=Na (23)
n=2 , R=Na (24)
n=1 , R=Me (25)
n=2 , R=Me (26)

Figure 13

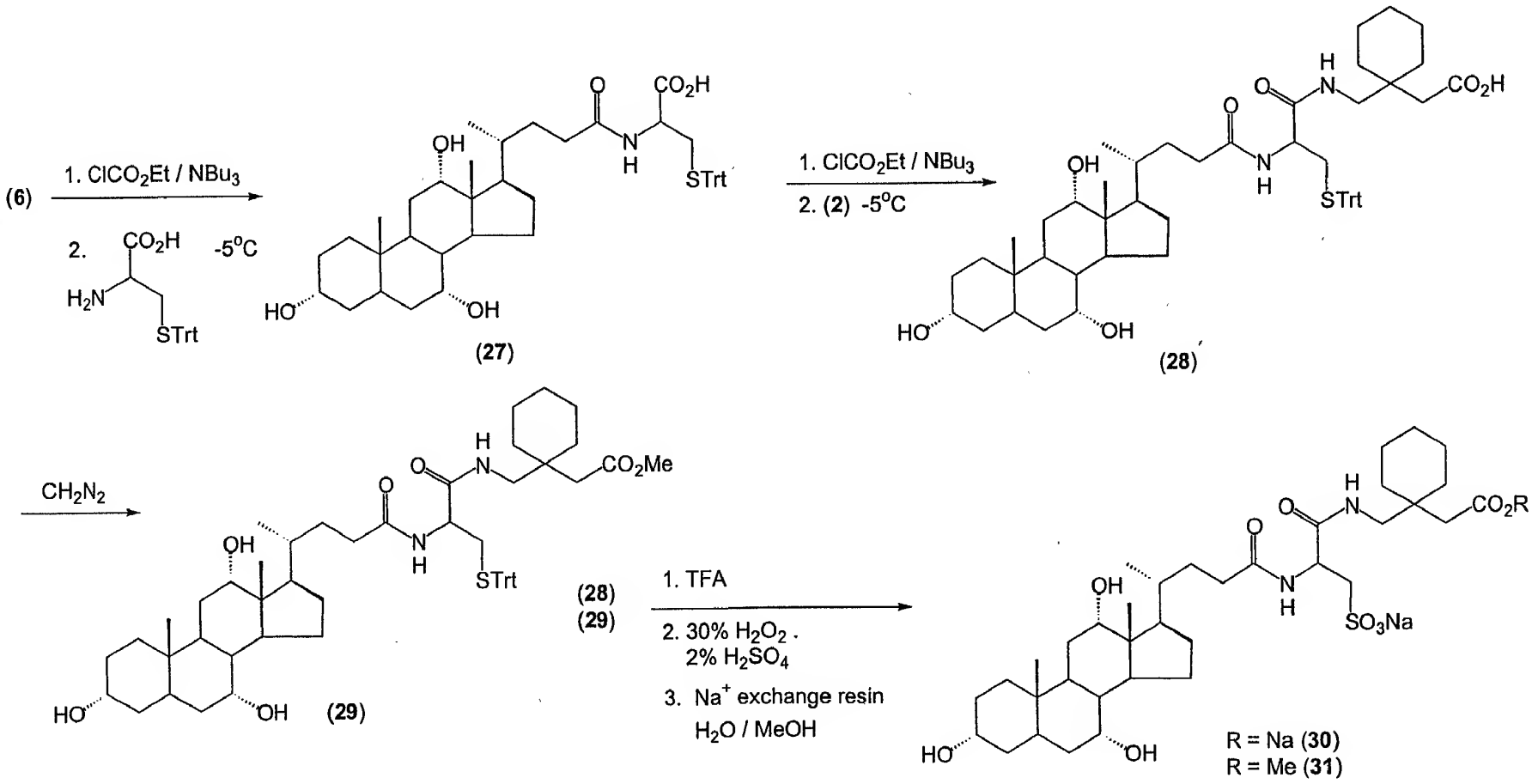


Figure 14

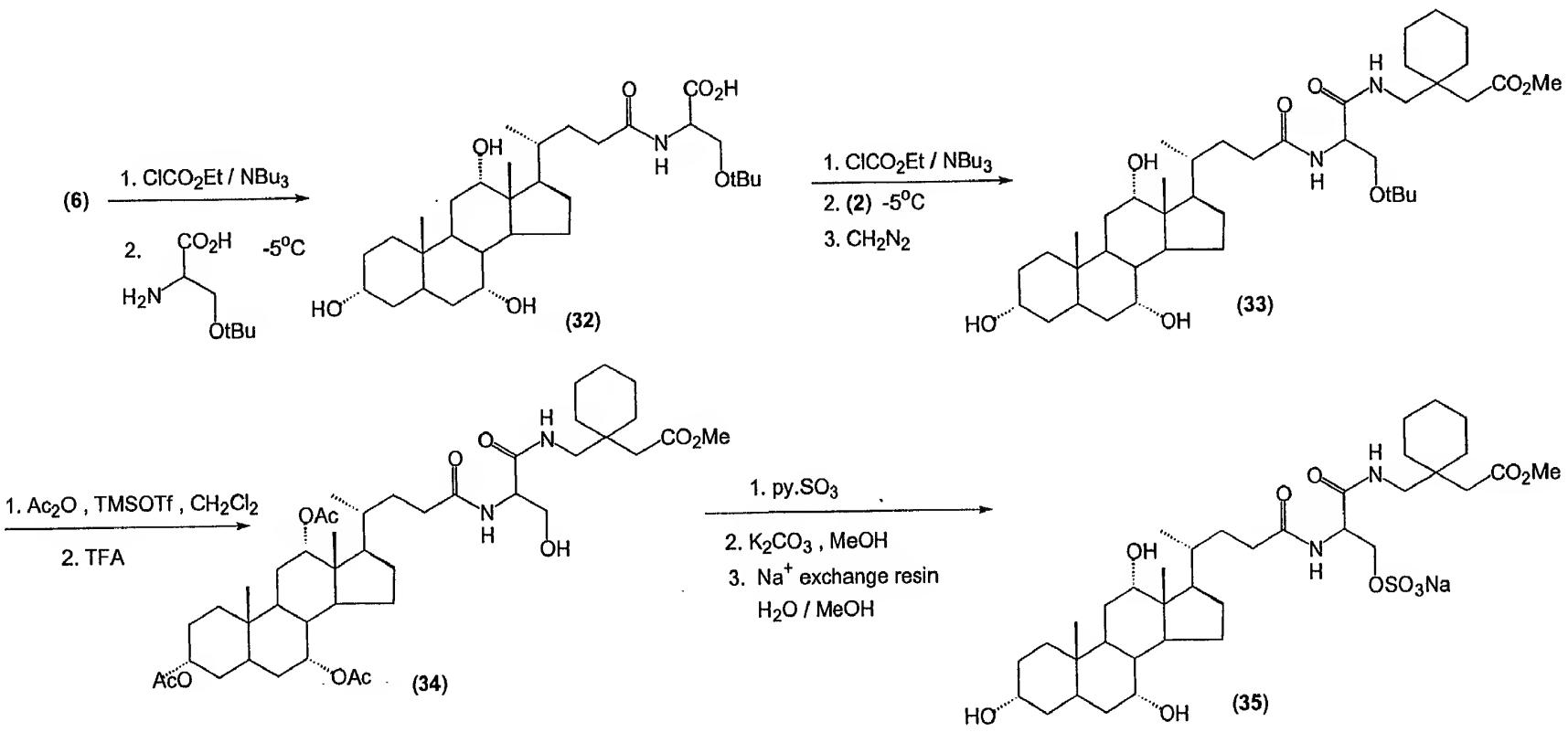


Figure 15

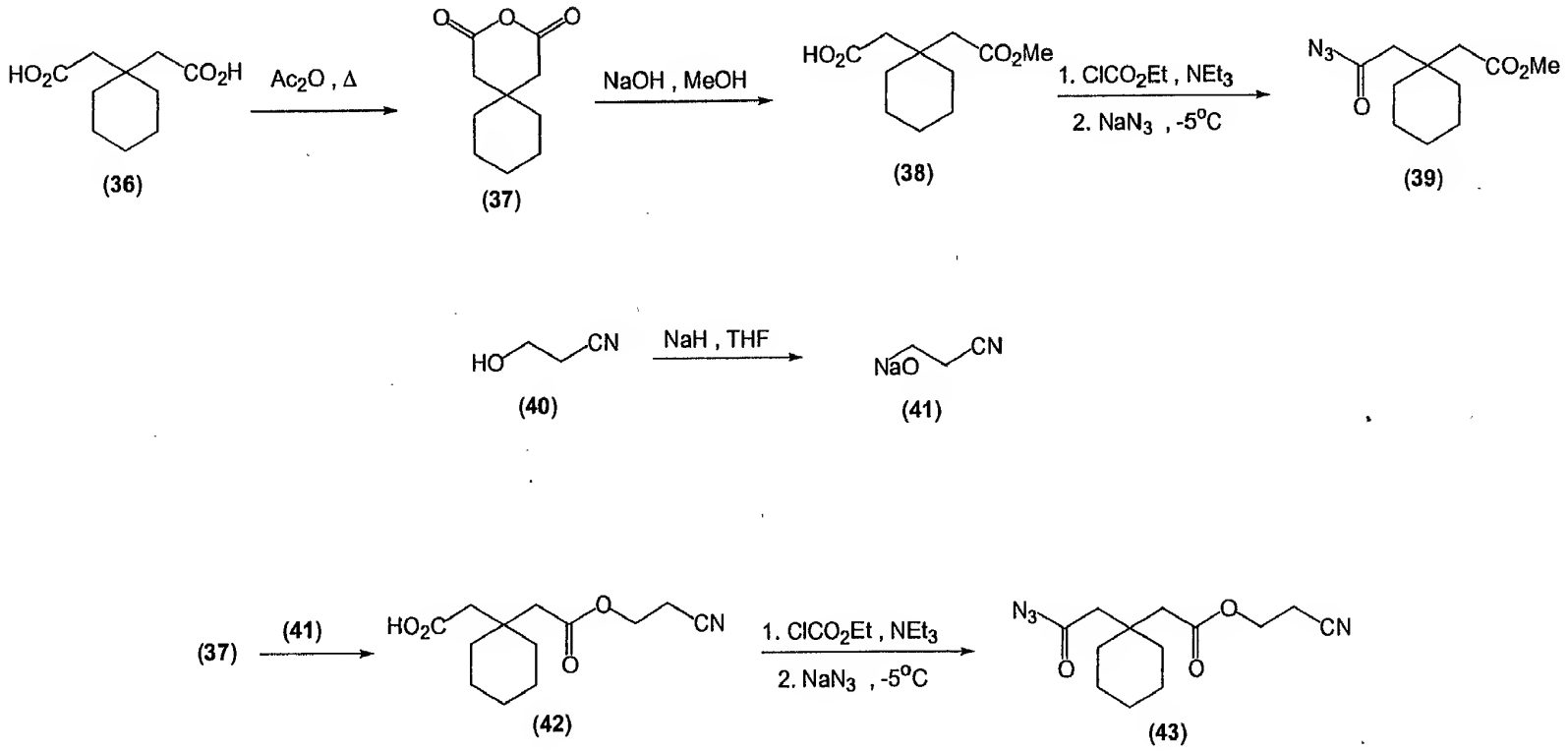


Figure 16

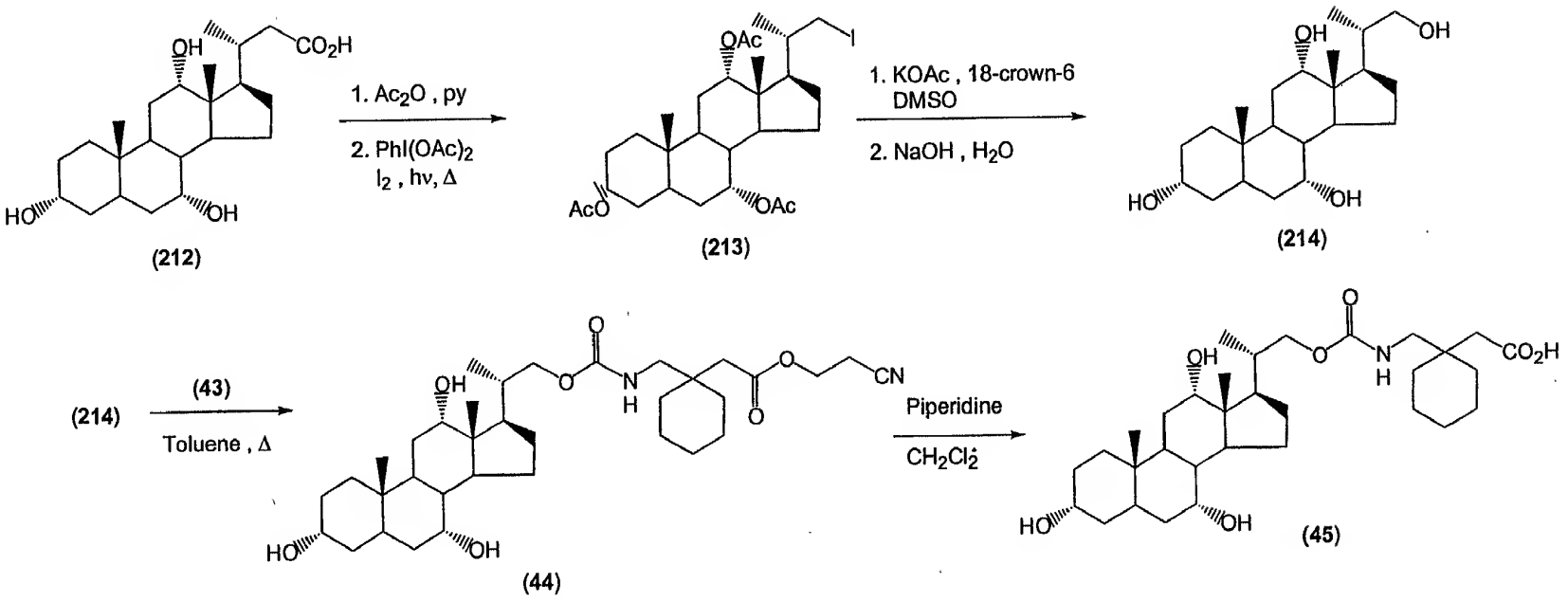

OH
CO2H
HO
OH
(212)
1. Ac2O , py
2. PhI(OAc)2
I2 , hv, Δ
OAc
I
AcO
OAc
(213)
1. KOAc , 18-crown-6
DMSO
2. NaOH , H2O
OH
OH
HO
OH
(214)
(214)
(43)
Toluene , Δ
OH
O
O
N
H
O
O
CN
HO
OH
(44)
Piperidine
CH2Cl2
O
OH
O
N
H
CO2H
HO
OH
(45)

Figure 17

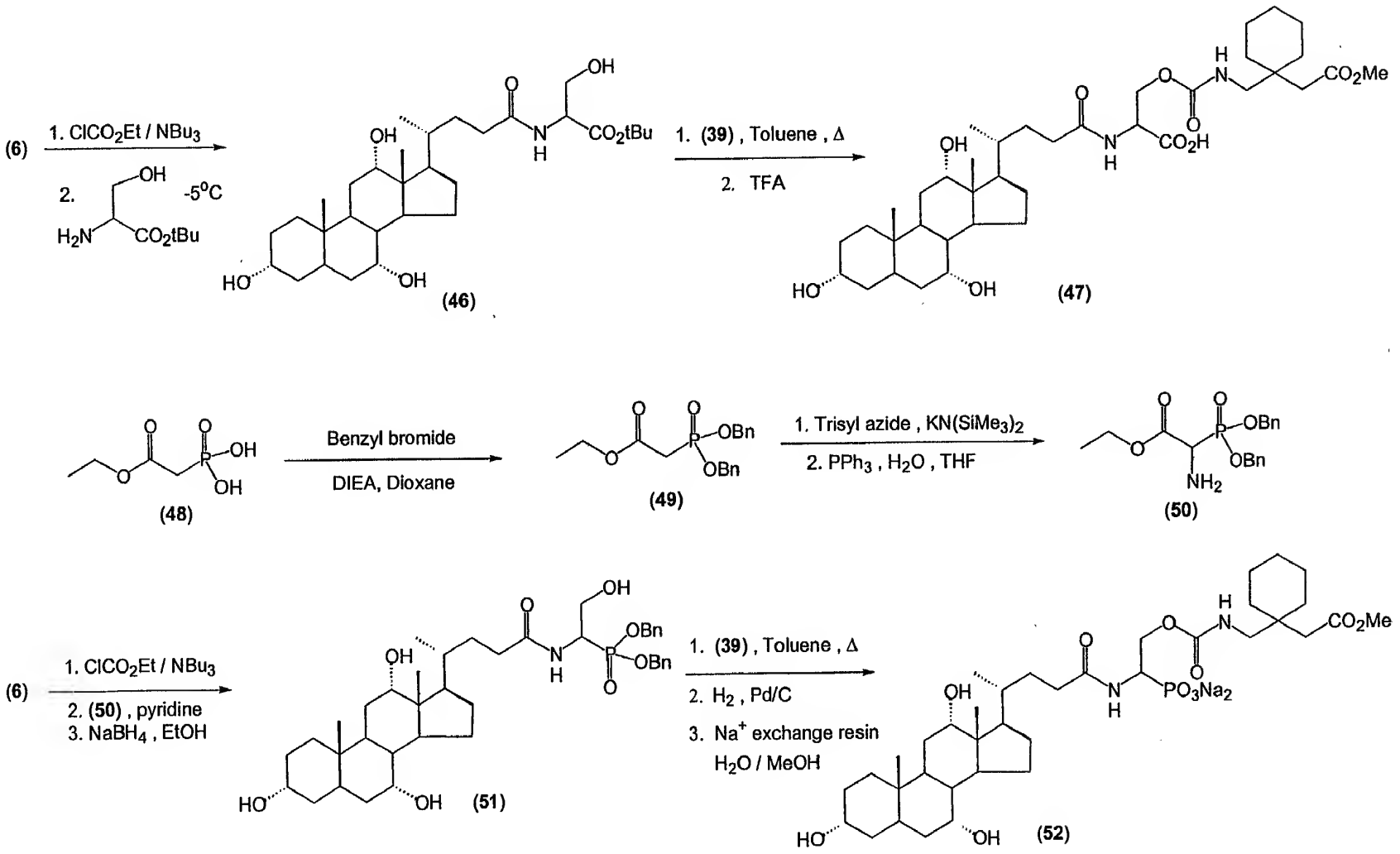

(6)
1. ClCO2Et / NBu3
2.
-5°C
H2N
CO2tBu
OH
(46)
1. (39) , Toluene , Δ
2. TFA
CO2H
CO2Me
(47)
(48)
Benzyl bromide
DIEA, Dioxane
OBn
(49)
1. Trisyl azide , KN(SiMe3)2
2. PPh3 , H2O , THF
NH2
(50)
(6)
1. ClCO2Et / NBu3
2. (50) , pyridine
3. NaBH4 , EtOH
(51)
1. (39) , Toluene , Δ
2. H2 , Pd/C
3. Na+ exchange resin
H2O / MeOH
PO3Na2
(52)

Figure 18

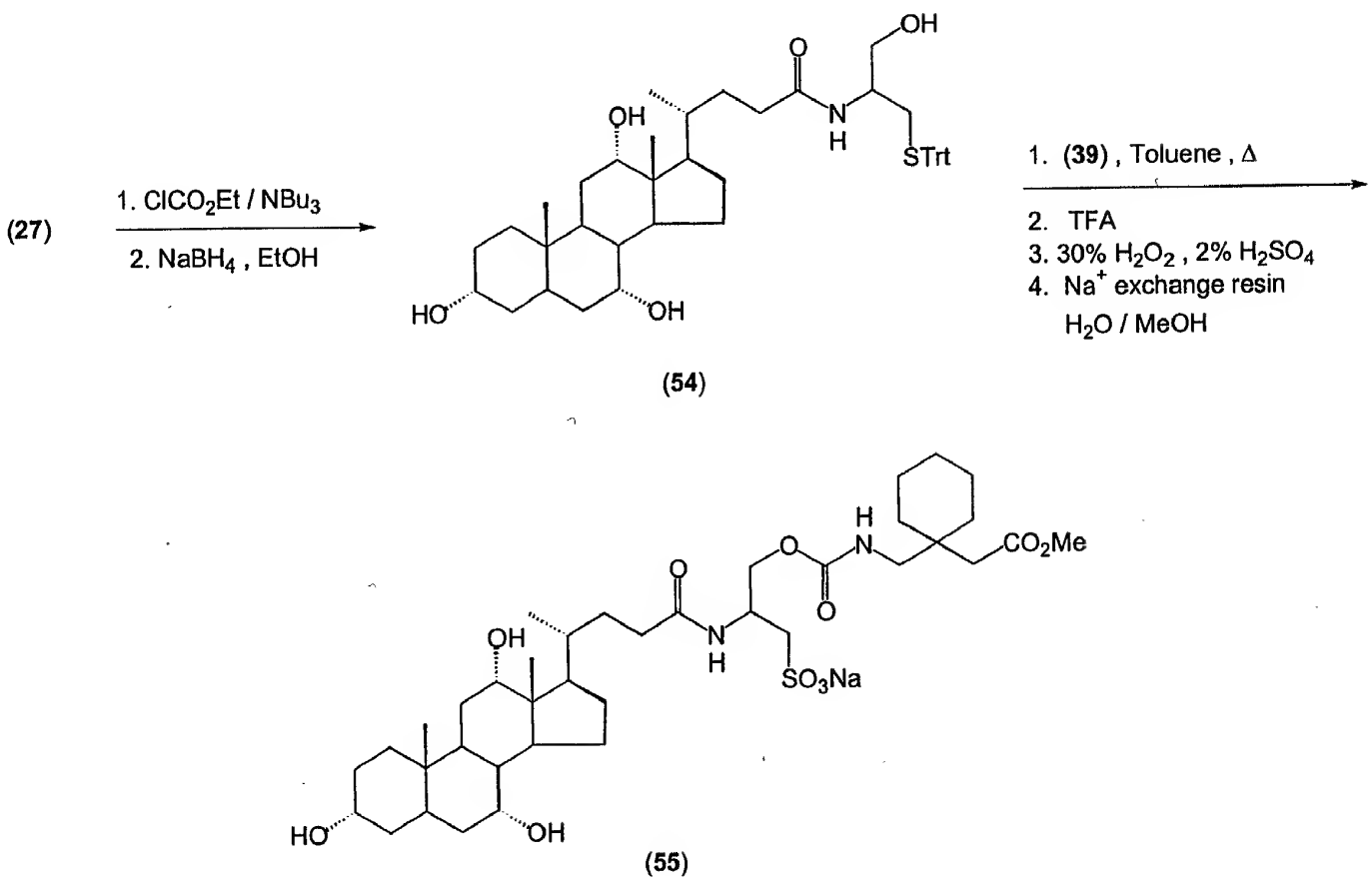


Figure 19

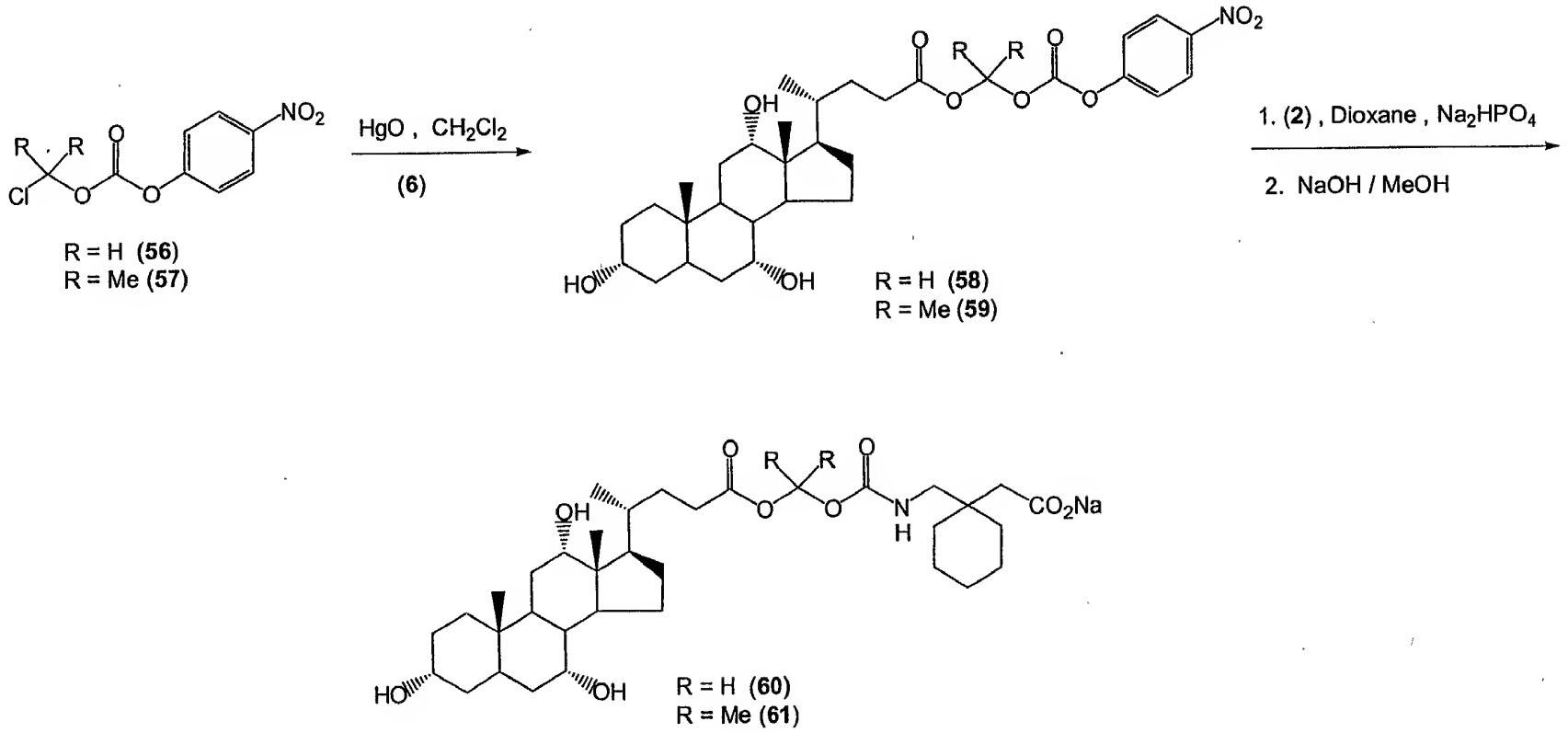

NO2
R
R
Cl
O
O
O
HgO , CH2Cl2
(6)
R = H (56)
R = Me (57)
OH
HO
OH
R = H (58)
R = Me (59)
1. (2) , Dioxane , Na2HPO4
2. NaOH / MeOH
N
H
CO2Na
R = H (60)
R = Me (61)

Figure 20

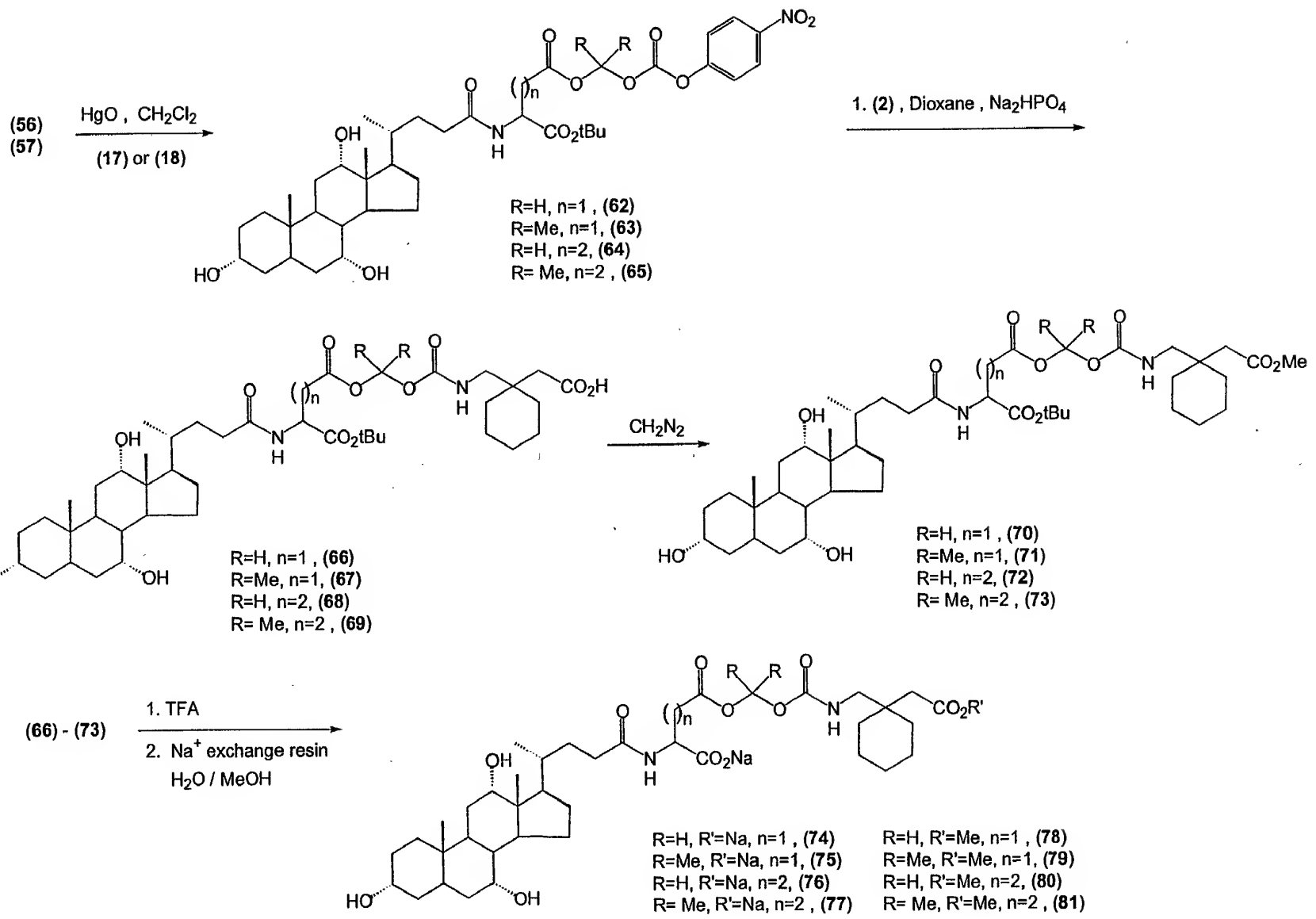


Figure 21

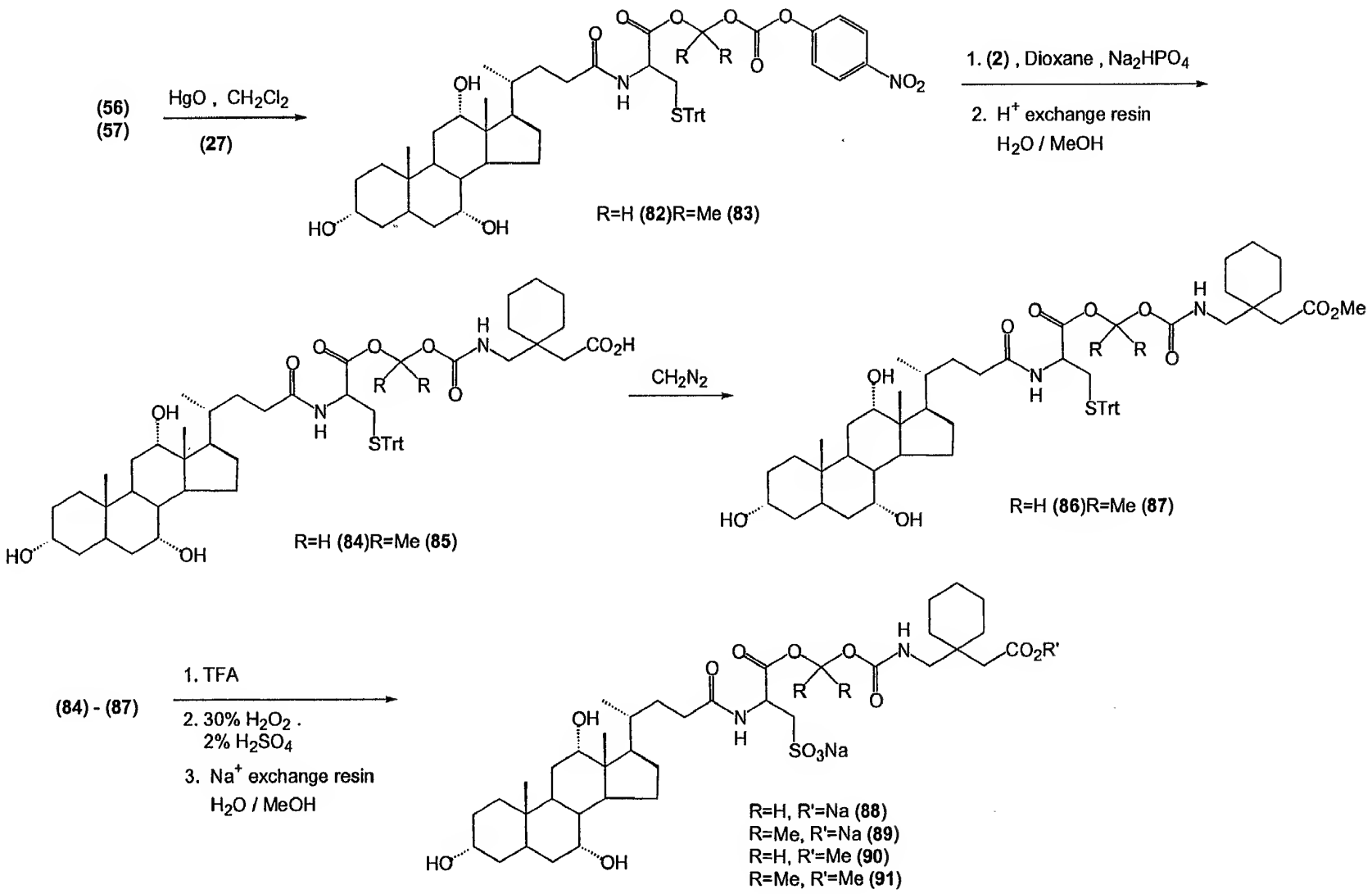
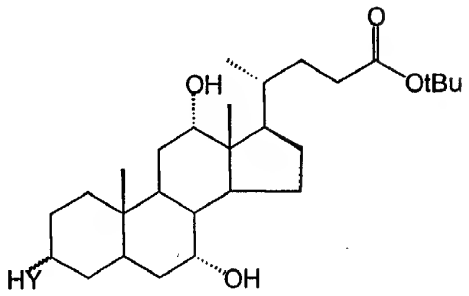
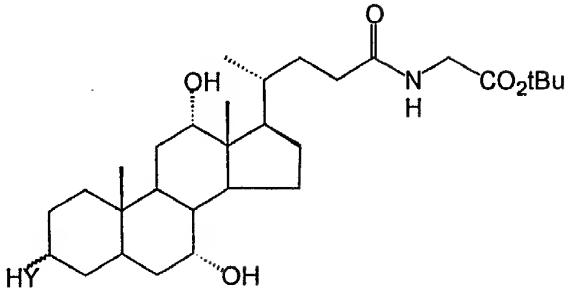


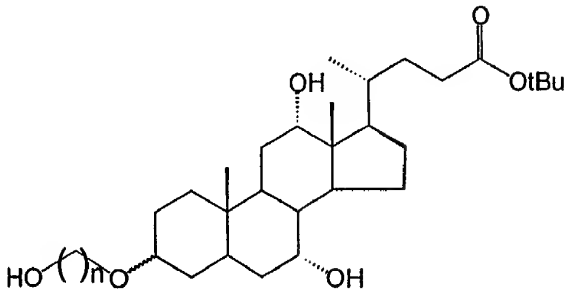
Figure 22



Y= 3α-O (**92**)
Y= 3β-O (**93**)
Y= 3α-NH (**94**)
Y= 3β-NH (**95**)

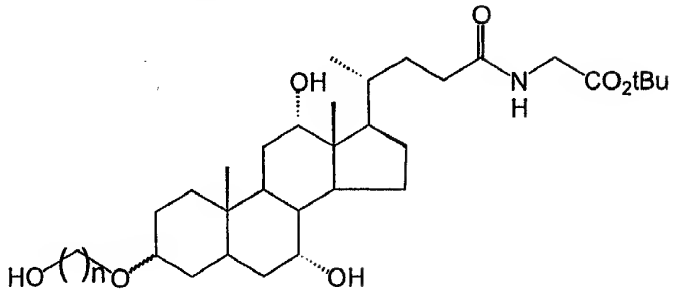


Y= 3α-O (**96**)
Y= 3β-O (**97**)
Y= 3α-NH (**98**)
Y= 3β-NH (**99**)



n = 1-5

3α-O (**100**)
3β-O (**101**)



n = 1-5

3α-O (**102**)
3β-O (**103**)

Compounds (**92**) - (**103**) prepared following methods described in co-pending application "Bile Acid-Derived Compounds for Enhancing Oral Absorption and Systemic Bioavailability of Drugs" assigned to XenoPort, Inc.

Figure 23

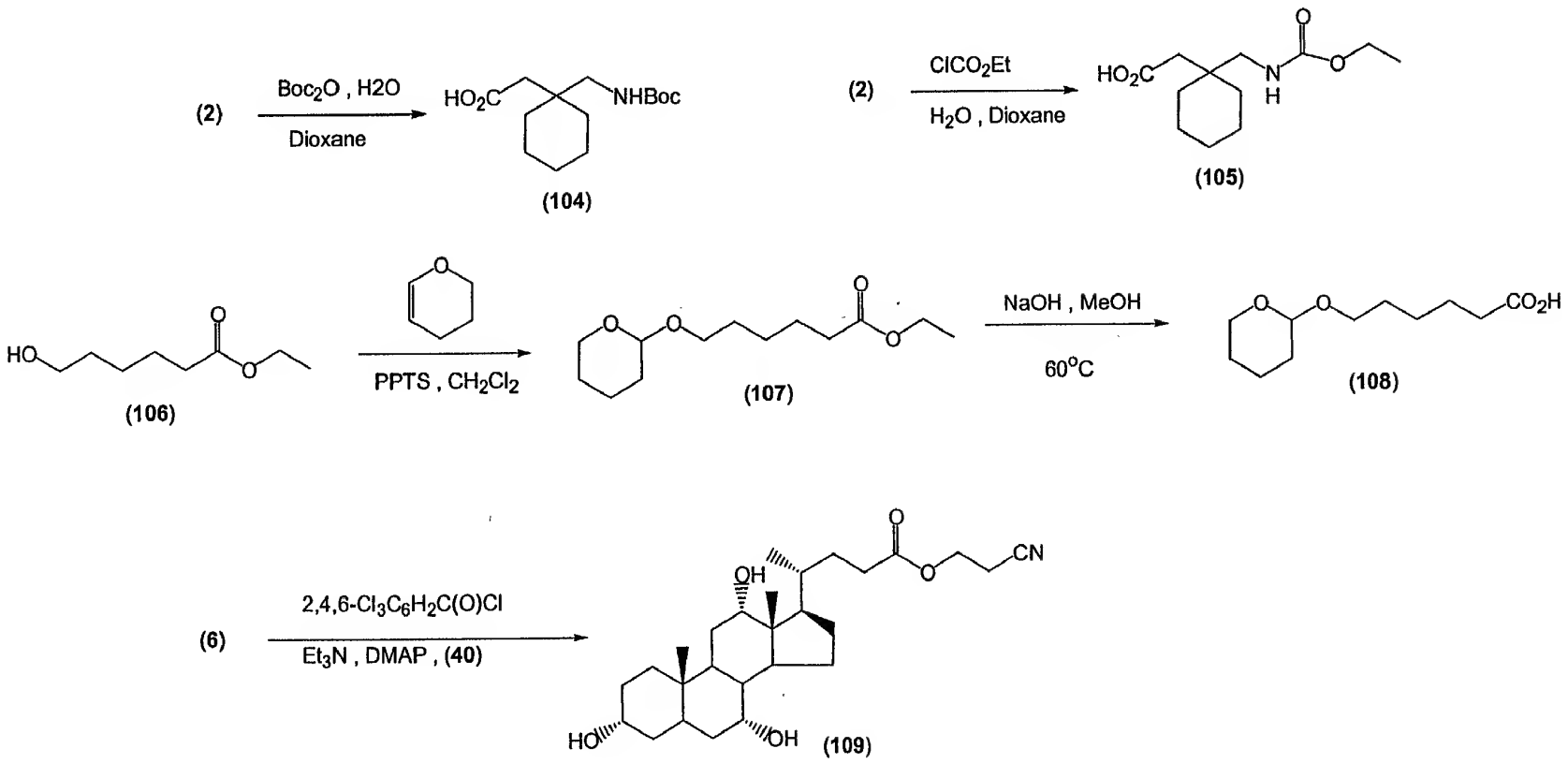


Figure 24

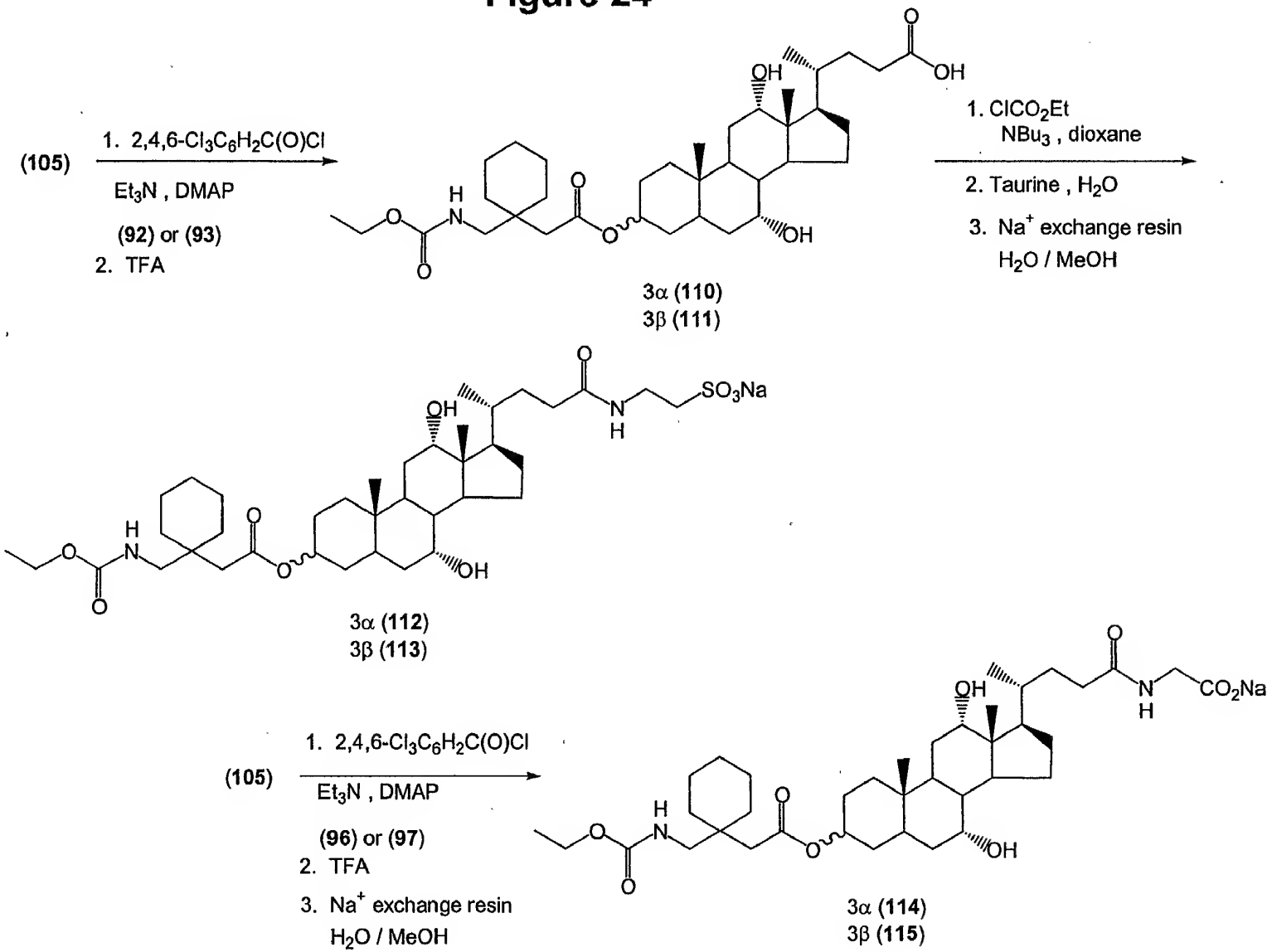

(105)
1. 2,4,6-Cl3C6H2C(O)Cl
Et3N , DMAP
(92) or (93)
2. TFA
3α (110)
3β (111)
1. ClCO2Et
NBu3 , dioxane
2. Taurine , H2O
3. Na+ exchange resin
H2O / MeOH
3α (112)
3β (113)
(105)
1. 2,4,6-Cl3C6H2C(O)Cl
Et3N , DMAP
(96) or (97)
2. TFA
3. Na+ exchange resin
H2O / MeOH
3α (114)
3β (115)

Figure 25

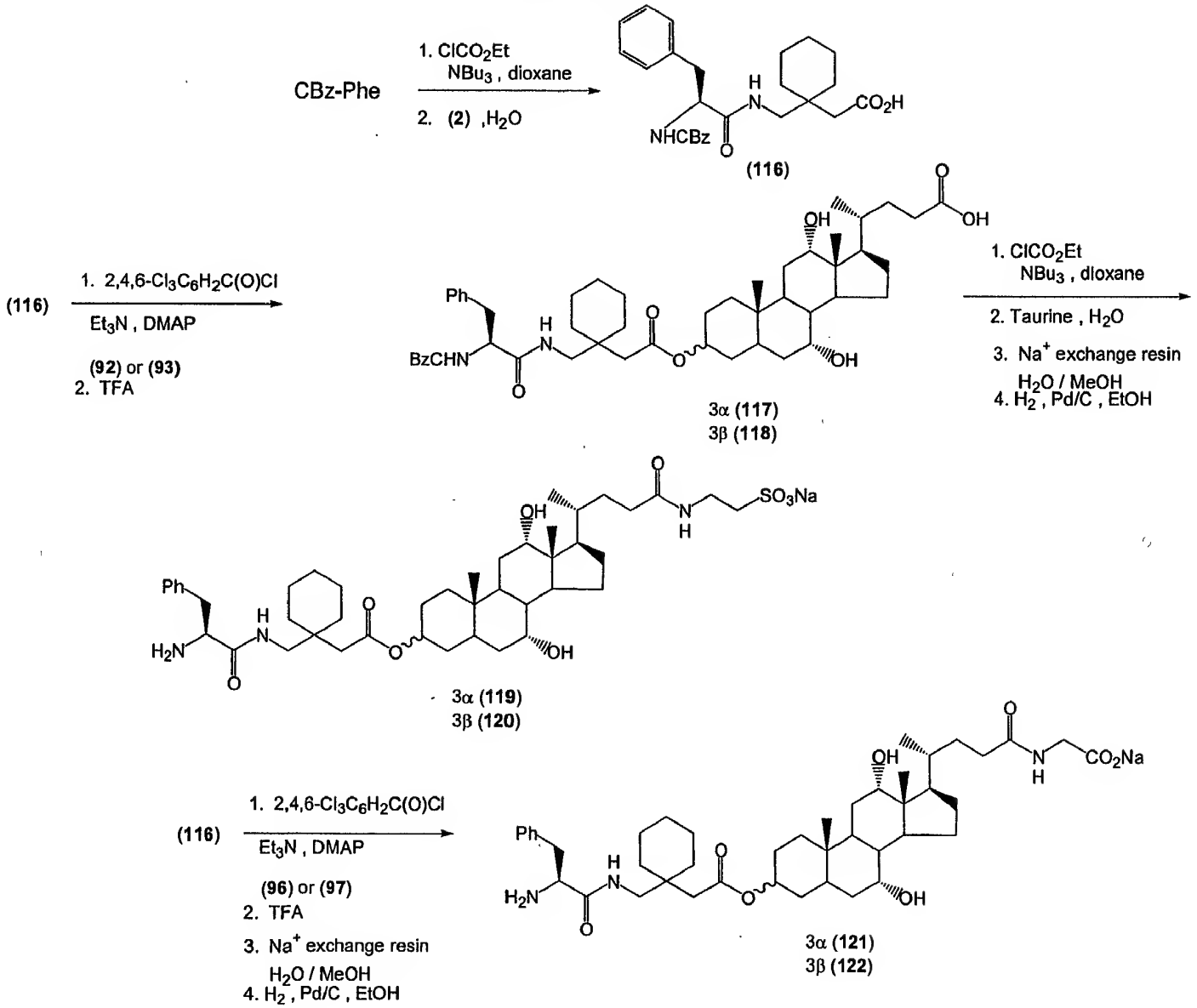

CBz-Phe
1. ClCO2Et
NBu3 , dioxane
2. (2) ,H2O
NHCBz
CO2H
(116)
(116)
1. 2,4,6-Cl3C6H2C(O)Cl
Et3N , DMAP
(92) or (93)
2. TFA
BzCHN
Ph
OH
OH
3α (117)
3β (118)
1. ClCO2Et
NBu3 , dioxane
2. Taurine , H2O
3. Na+ exchange resin
H2O / MeOH
4. H2 , Pd/C , EtOH
SO3Na
H2N
3α (119)
3β (120)
(116)
1. 2,4,6-Cl3C6H2C(O)Cl
Et3N , DMAP
(96) or (97)
2. TFA
3. Na+ exchange resin
H2O / MeOH
4. H2 , Pd/C , EtOH
CO2Na
3α (121)
3β (122)

Figure 26

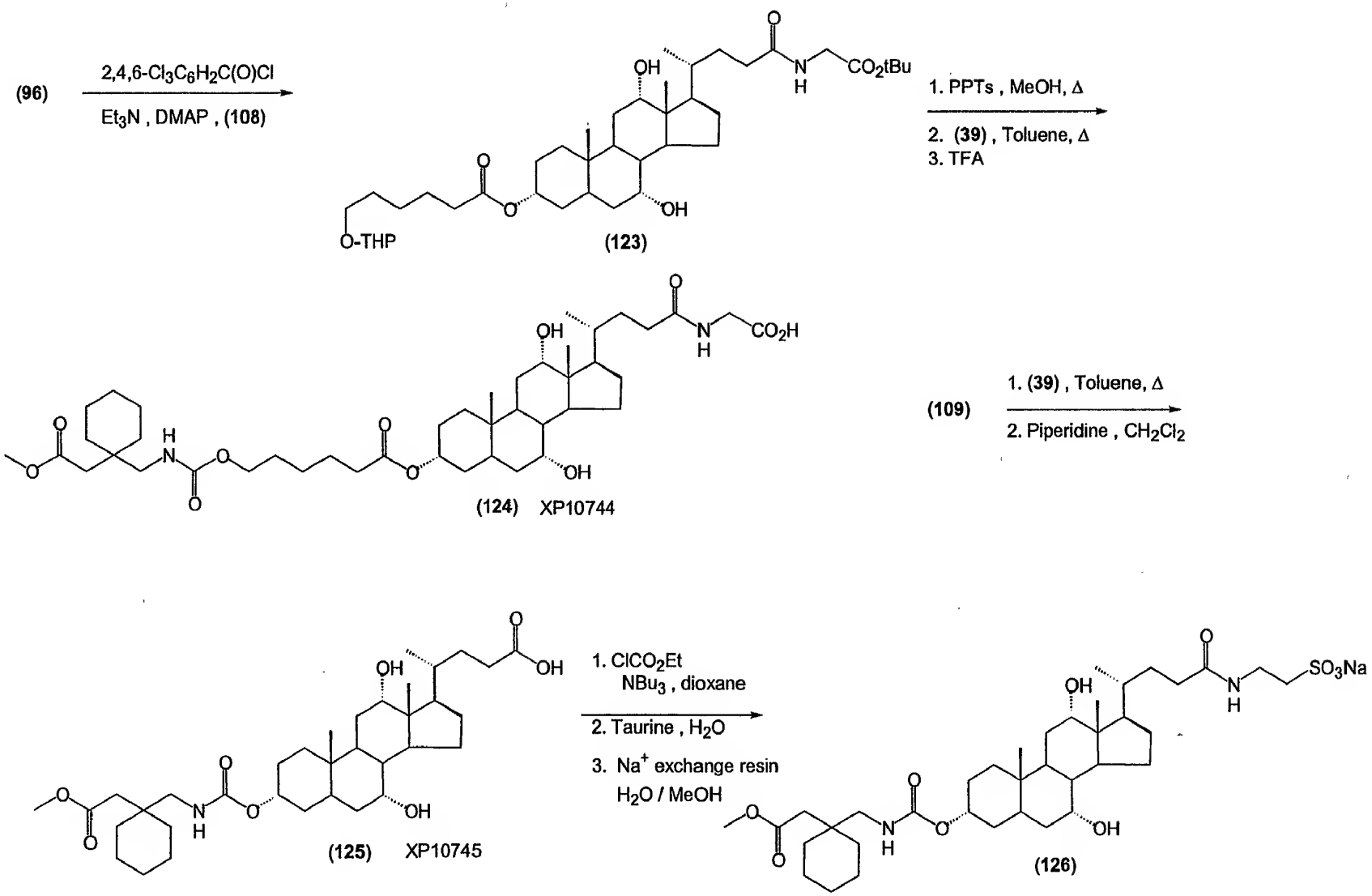

(96)
2,4,6-Cl3C6H2C(O)Cl
Et3N , DMAP , (108)
OH
N
H
CO2tBu
O-THP
OH
(123)
1. PPTs , MeOH, Δ
2. (39) , Toluene, Δ
3. TFA
OH
N
H
CO2H
OH
(124) XP10744
(109)
1. (39) , Toluene, Δ
2. Piperidine , CH2Cl2
OH
OH
(125) XP10745
1. ClCO2Et
NBu3 , dioxane
2. Taurine , H2O
3. Na+ exchange resin
H2O / MeOH
SO3Na
OH
(126)

Figure 27

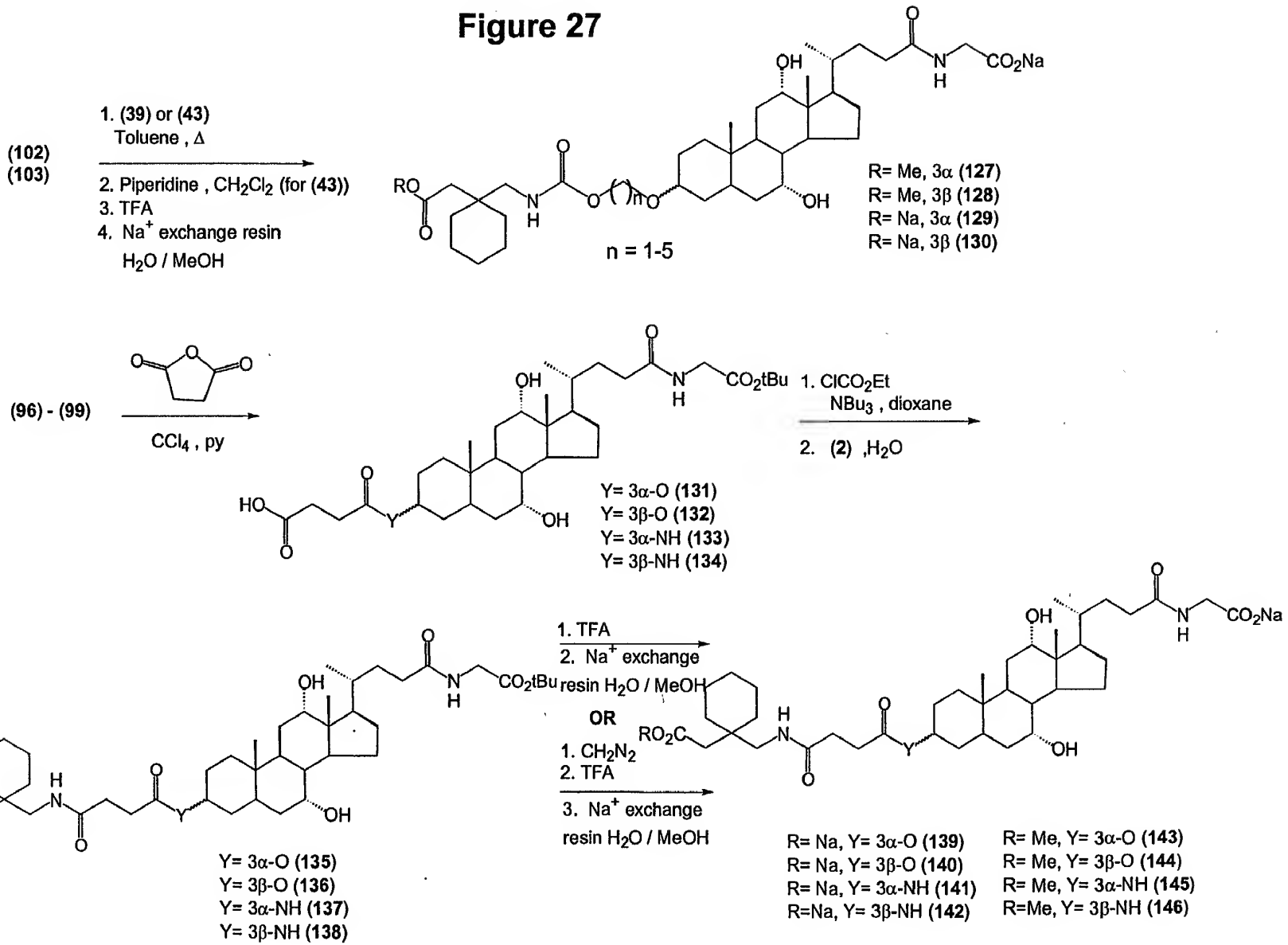
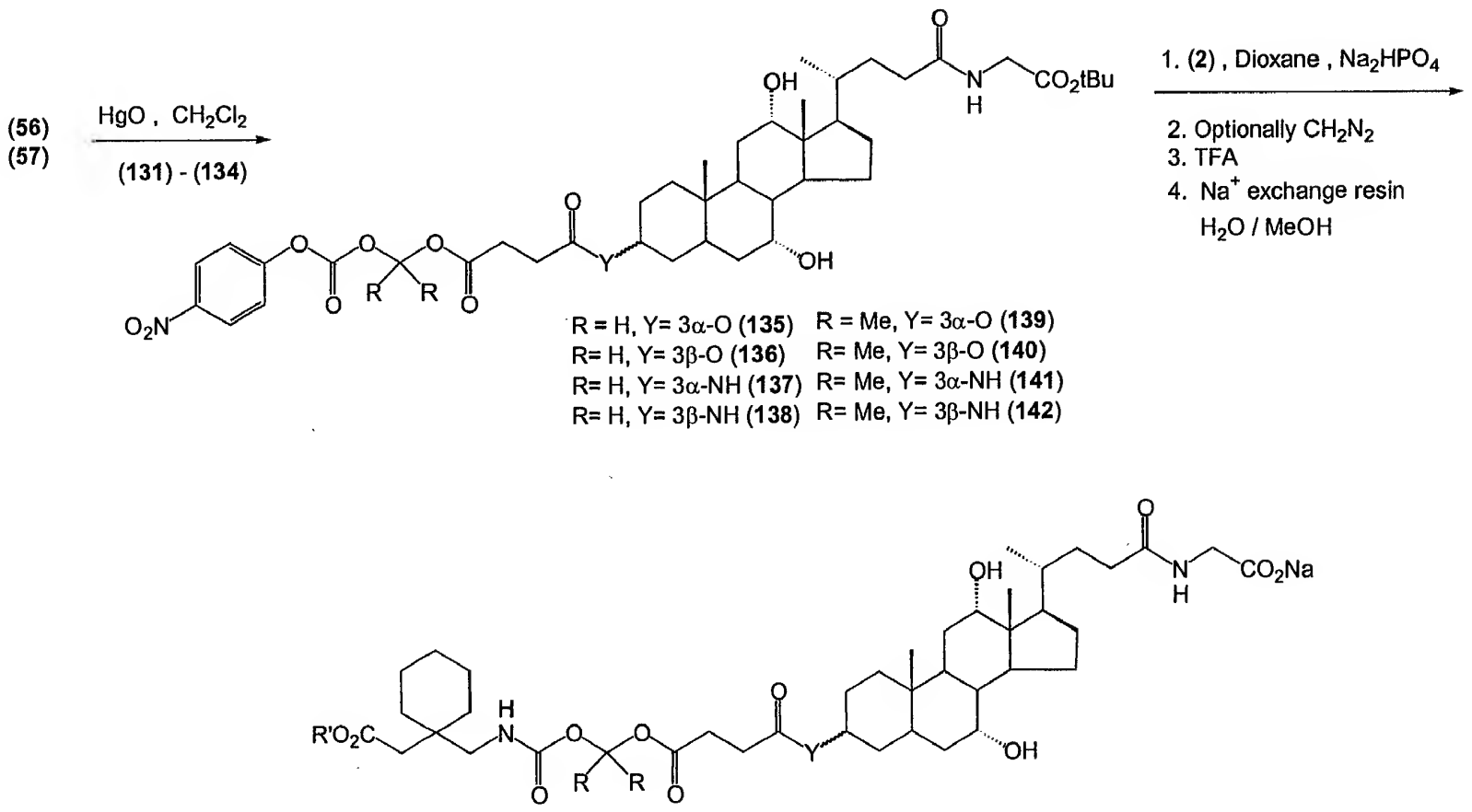

1. (39) or (43)
Toluene , Δ
(102)
(103)
2. Piperidine , CH_2Cl_2 (for (43))
3. TFA
4. Na^+ exchange resin
H_2O / MeOH
n = 1-5
R= Me, 3α (127)
R= Me, 3β (128)
R= Na, 3α (129)
R= Na, 3β (130)
(96) - (99)
CCl_4 , py
1. $ClCO_2Et$
NBu_3 , dioxane
2. (2) ,H_2O
Y= 3α-O (131)
Y= 3β-O (132)
Y= 3α-NH (133)
Y= 3β-NH (134)
1. TFA
2. Na^+ exchange resin H_2O / MeOH
OR
1. CH_2N_2
2. TFA
3. Na^+ exchange resin H_2O / MeOH
Y= 3α-O (135)
Y= 3β-O (136)
Y= 3α-NH (137)
Y= 3β-NH (138)
R= Na, Y= 3α-O (139)
R= Na, Y= 3β-O (140)
R= Na, Y= 3α-NH (141)
R=Na, Y= 3β-NH (142)
R= Me, Y= 3α-O (143)
R= Me, Y= 3β-O (144)
R= Me, Y= 3α-NH (145)
R=Me, Y= 3β-NH (146)

Figure 28



R'= Na, R = H, Y= 3α-O (**143**) R'= Na, R = Me, Y= 3α-O (**147**) R'= Me, R = H, Y= 3α-O (**151**) R'= Me, R = Me, Y= 3α-O (**155**)
R'= Na, R= H, Y= 3β-O (**144**) R'= Na, R= Me, Y= 3β-O (**148**) R'= Me, R= H, Y= 3β-O (**152**) R'= Me, R= Me, Y= 3β-O (**156**)
R'= Na, R= H, Y= 3α-NH (**145**) R'= Na, R= Me, Y= 3α-NH (**149**) R'= Me, R= H, Y= 3α-NH (**153**) R'= Me, R= Me, Y= 3α-NH (**157**)
R'= Na, R= H, Y= 3β-NH (**146**) R'= Na, R= Me, Y= 3β-NH (**150**) R'= Me, R= H, Y= 3β-NH (**154**) R'= Me, R= Me, Y= 3β-NH (**158**)

Figure 29

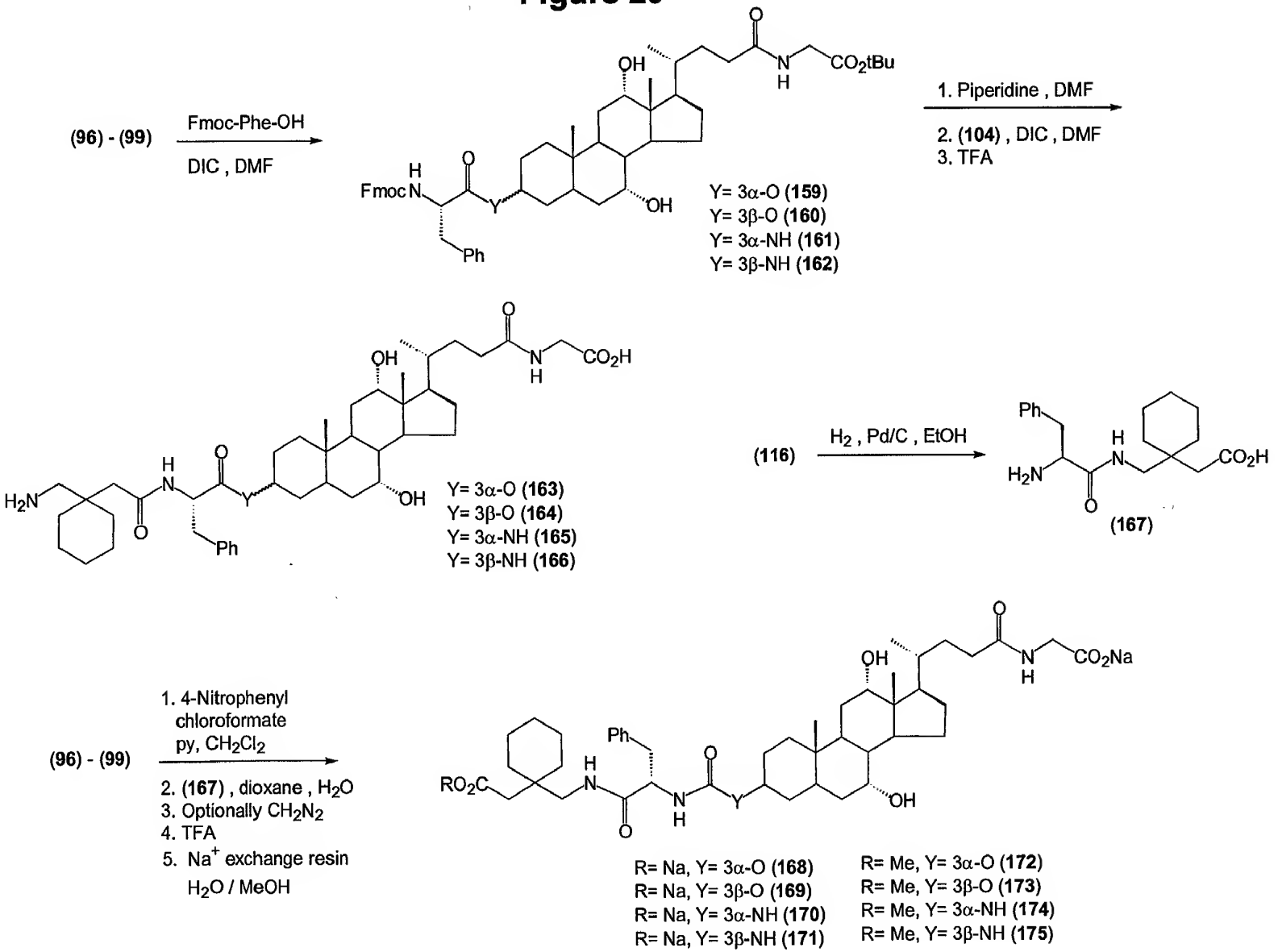

(96) - (99)
Fmoc-Phe-OH
DIC , DMF
1. Piperidine , DMF
2. (104) , DIC , DMF
3. TFA
Y= 3α-O (159)
Y= 3β-O (160)
Y= 3α-NH (161)
Y= 3β-NH (162)
Y= 3α-O (163)
Y= 3β-O (164)
Y= 3α-NH (165)
Y= 3β-NH (166)
(116)
H2 , Pd/C , EtOH
(167)
(96) - (99)
1. 4-Nitrophenyl chloroformate py, CH2Cl2
2. (167) , dioxane , H2O
3. Optionally CH2N2
4. TFA
5. Na+ exchange resin H2O / MeOH
R= Na, Y= 3α-O (168)
R= Na, Y= 3β-O (169)
R= Na, Y= 3α-NH (170)
R= Na, Y= 3β-NH (171)
R= Me, Y= 3α-O (172)
R= Me, Y= 3β-O (173)
R= Me, Y= 3α-NH (174)
R= Me, Y= 3β-NH (175)

Figure 30

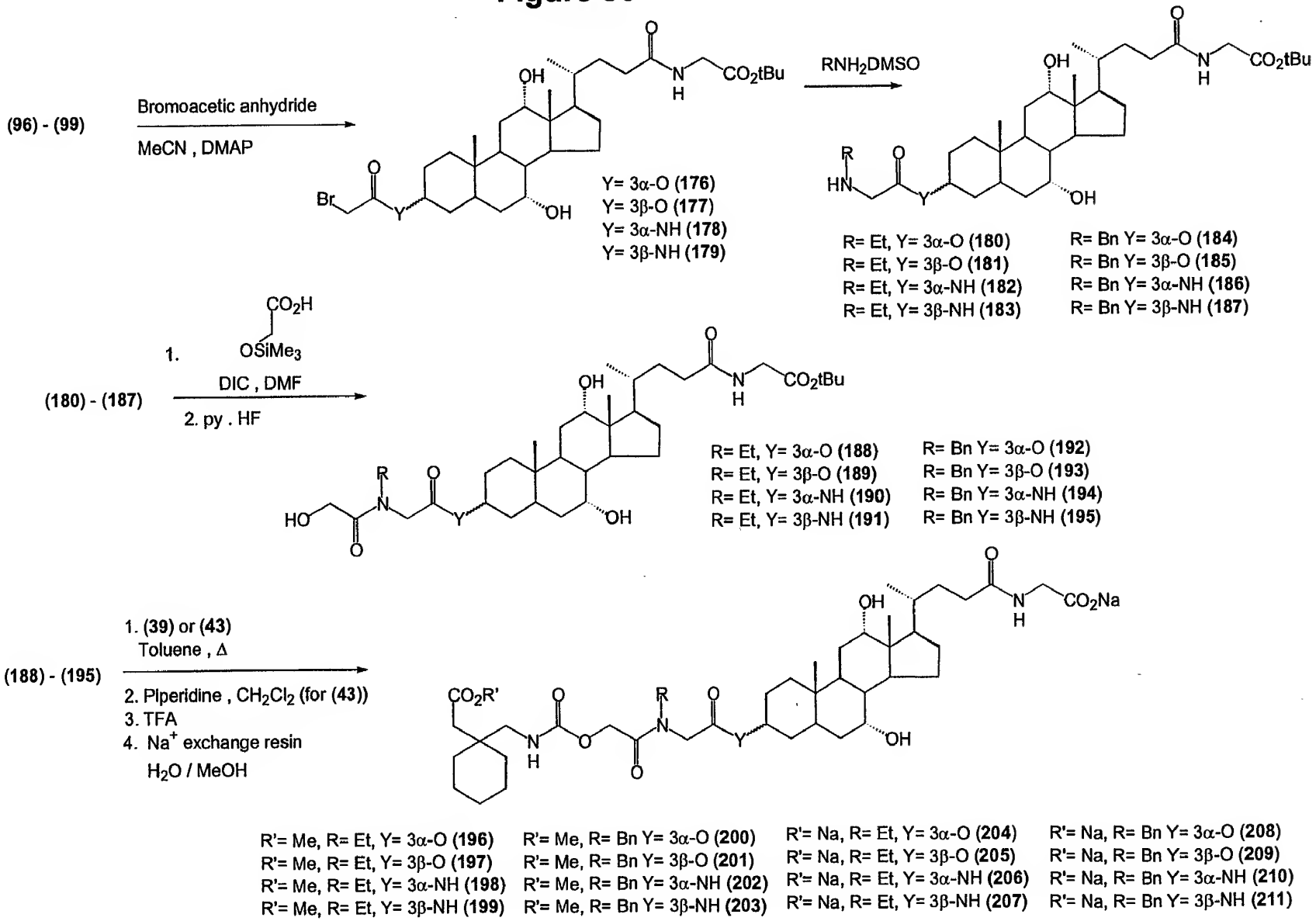


Figure 31

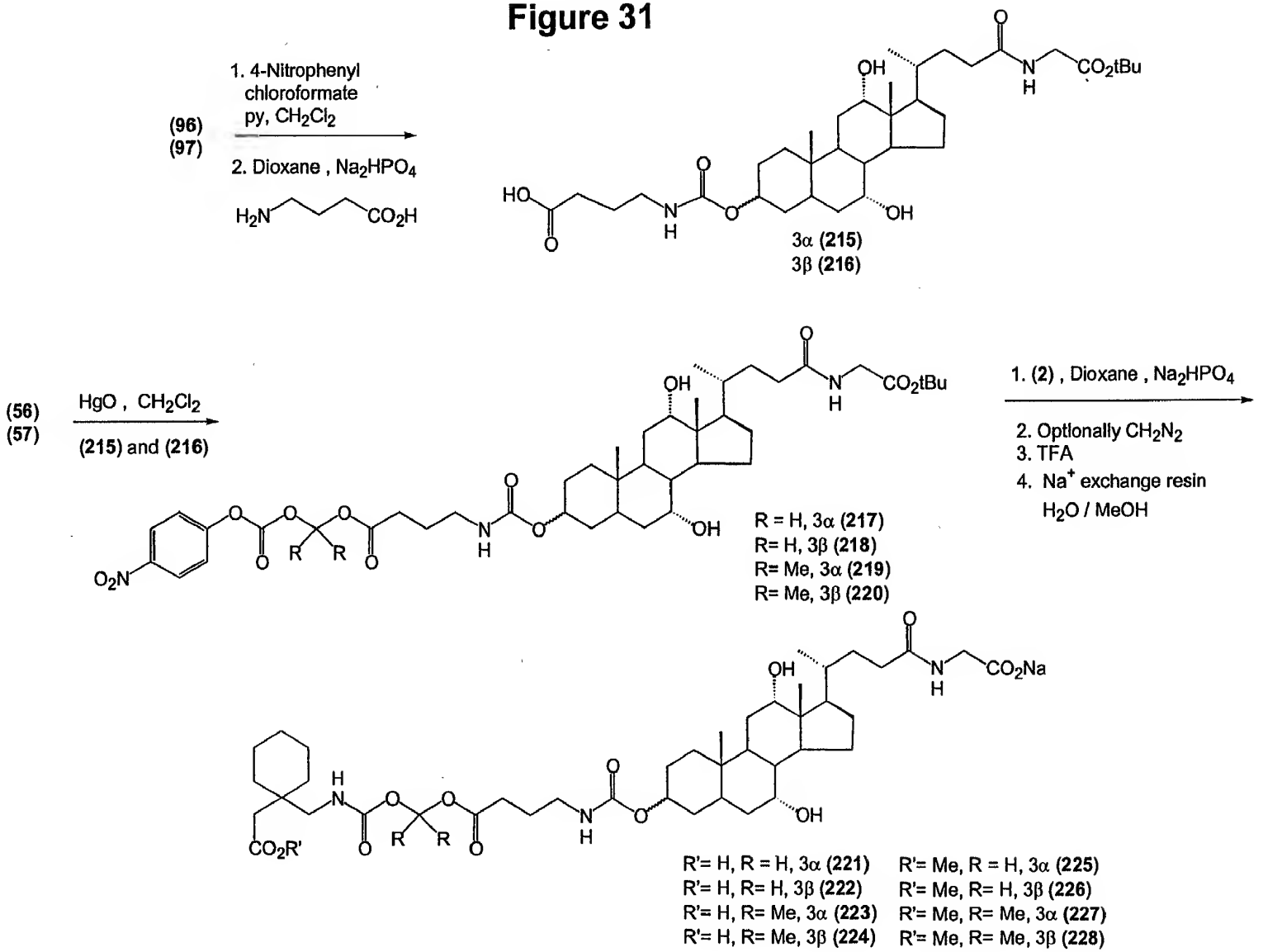

1. 4-Nitrophenyl chloroformate py, CH_2Cl_2
(96)
(97)
2. Dioxane , Na_2HPO_4
H_2N
CO_2H
HO
O
N
H
O
OH
OH
N
H
CO_2tBu
3α (215)
3β (216)
(56)
(57)
HgO , CH_2Cl_2
(215) and (216)
O_2N
R = H, 3α (217)
R= H, 3β (218)
R= Me, 3α (219)
R= Me, 3β (220)
1. (2) , Dioxane , Na_2HPO_4
2. Optionally CH_2N_2
3. TFA
4. Na^+ exchange resin
H_2O / MeOH
CO_2Na
CO_2R'
R'= H, R = H, 3α (221)
R'= H, R= H, 3β (222)
R'= H, R= Me, 3α (223)
R'= H, R= Me, 3β (224)
R'= Me, R = H, 3α (225)
R'= Me, R= H, 3β (226)
R'= Me, R= Me, 3α (227)
R'= Me, R= Me, 3β (228)

Figure 32

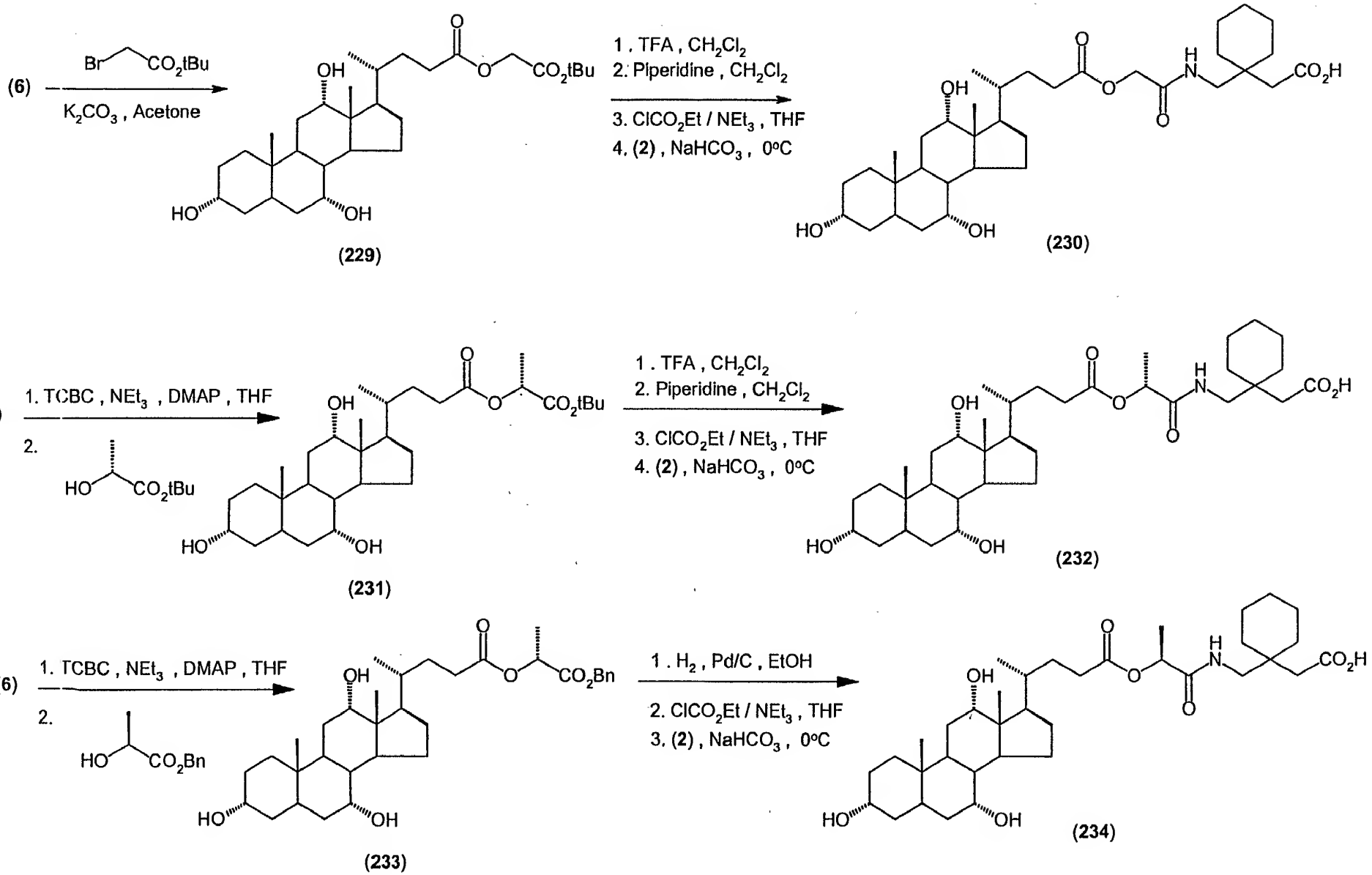
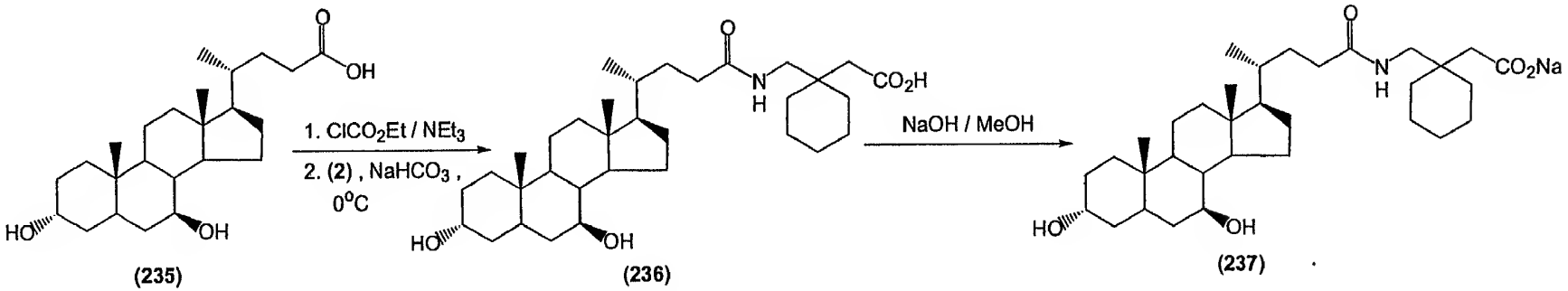


Figure 33


O
OH
HO
OH
(235)
1. ClCO2Et / NEt3
2. (2) , NaHCO3 ,
0°C
O
N
H
CO2H
HO
OH
(236)
NaOH / MeOH
O
N
H
CO2Na
HO
OH
(237)